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VOLUME I

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PREFACE

In assembling the titles for this and the forthcoming volumes of *Advances in Surgery* the Editors have borne in mind the fact that progress in this area today owes much to developments in other fields which have been applied to surgical problems. The use of antimicrobial agents and the discovery of the importance of recognizing and correcting certain nutritional deficiencies, to mention only two examples, have had tremendous effects on surgical results by making procedures safer to carry out and also by permitting a more aggressive attack in cases previously considered inoperable. These volumes will therefore contain articles covering not only what may be called purely surgical subjects but also developments in other fields which may contribute to surgical therapy.

November 1948 — WILLIAM DEWITT ANDRUS, M.D.

CONTENTS

Recent Advances in Traumatic Shock

JACOB FINE
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Introduction

Impressive progress in our understanding of traumatic shock has been made in recent years Since the fundamental mechanism of the disorder still remains an enigma, it would be futile to attempt a definition of the syndrome But a descriptive statement of the characteristic features of the condition, to which all students of the problem will agree, may serve as a point of departure for a critical analysis of some of the evidence brought forward during the past five years

Traumatic shock is a state of acute collapse of the peripheral circulation, the manifestations of which are (*1*) reduced velocity of blood flow through most, if not all, tissues (*2*) greatly diminished cardiac output (*3*) decreased circulating blood volume (*4*) sharp fall in the oxygen concentration of the venous blood (*5*) increase in acid metabolites and decrease in carbon dioxide combining capacity of the blood (*6*) low or falling blood pressure. It has been shown that all of these changes are present in experimental animals regard less of the precipitating cause of the shock state, and recently they have been verified in man (16) The consequences of their presence are diminished or absent excretion of urine, muscular weakness diminished oxygen consumption and metabolic rate and sympathetic nervous system dominance the last mentioned is evidenced by vasoconstriction pale, cyanotic, and cooler than normal skin and mucous membranes sweating, and tachycardia. Other signs such as restless-

ness, nausea decreased pain sensitivity are too inconstant to permit their inclusion in a list of the classic manifestations of shock.

It is at once obvious that the body economy must disintegrate rapidly in such circumstances, as experience demonstrates. Whether the lethal effects of shock derive from simultaneous widespread collapse of cellular function or from the loss of functional integrity of a controlling organ or tissue has not been definitely demonstrated.

There is universal agreement that typical traumatic shock results from a variety of causes that have no common denominator Thus the usual cause, i.e loss of whole blood or plasma, is apparently not operative in shock resulting from overwhelming toxemia of bacterial origin or chemical poisons for while blood replacement therapy, if applied in time is effective in shock due to hemorrhage, it is quite useless no matter when applied in shock due to overwhelming infection or lethal doses of poison. We are therefore obliged to accept more than one etiologic agent, which has led some investigators to differentiate one type of traumatic shock from another Evidence to sustain this thesis is derived in part from pathologic data. Thus changes in the liver intestines and adrenal gland resulting from severe burns may not be seen when death results from simple hemorrhagic shock. Such facts serve to confuse rather than clarify the issue It is to be expected that each of the precipitating agents may inflict its own variety of damage in addition to having the common property of attacking the biologic system which is involved in the development of the shock state The clinical picture will thus differ in accordance with the special point or points of attack of the initiating agent but the fundamental disorder in the circulation presumably is the same in all. Moreover if the biologic system injured in shock involves a chemical chain reaction, for example, between the liver and the musculature of the arterioles and venules it is possible that one causative agent may affect the liver another the vascular musculature or both liver and musculature in either case the result is the same The fact that the site of final action of any agent is on the peripheral vascular mechanism whether this is injured directly or indirectly probably explains the fact that until recently the search for the basic mechanisms of shock has been confined largely to a study of the circulation. Extravascular disturbances in specific tissues which may be responsible for the vascular collapse have received insufficient consideration.

The Capillary Leakage Hypothesis

Until shortly before World War II, it was generally believed that failure of the organism to respond to blood volume therapy was due to escape of the infused fluid, as well as the patient's own blood filtrate, through damaged capillaries, which were said to be more permeable. This was inferred from the fact that volume replacement therapy, effective if given early enough, was often ineffective if given late. Hence the damage to the capillaries was considered to be a function of time. This, however, cannot apply to shock due to toxemia, because significant volume deficiency frequently does not exist and fluid therapy is useless from the beginning. Such considerations make it obvious that if progress is to be forthcoming, incontrovertible proof of the validity of the capillary leakage hypothesis is imperative.

A dispassionate examination of the evidence (53) is, therefore, in order The theory assumes the existence of a *generalized* increase in capillary permeability, resulting from prolonged anoxia. Accordingly, extravasated plasma must be shown to be present (*1*) in all cases of shock regardless of the manner in which shock was produced —even in the absence of significant trauma, as, for example, in shock due to simple external bleeding, (*2*) not merely in areas of trauma but elsewhere as well, (*3*) regardless of whether infusions have been given. Finally and as complementary evidence, it must be shown that blood volume deficiency cannot be made good in spite of adequate fluid therapy

Certain points in this hypothesis are not in dispute. It is agreed that lethal losses of plasma may occur in burns, and that blood or plasma is lost in large volume into extensively damaged tissue or into extremities released from long-standing compression. It is also agreed that recovery occurs when resulting blood volume deficiencies are restored early, but that recovery does not occur when deficiencies are restored even lavishly but too late It is further agreed that in shock states resulting from local trauma, one can demonstrate a continuing loss of fluid into the injured area, especially in burns. Moreover, hemorrhage or fluid exudate is found in various untraumatized tissues, notably in the intestines and lungs.

Edema, except at the site of local injury, is an inconstant finding, when present, the fluid therapy given rather than the shock process

itself may account for its presence. For when no fluid therapy is given edema is absent or too slight to be significant. Hemorrhage signifies rupture of capillaries a condition which is not implicit in the concept of increased capillary permeability If capillary hemorrhage is to be regarded as relevant evidence it must be constantly found in significant volume in all instances of fatal shock, especially if transfusions have been given and not necessarily confined to one or several tissues.

Finally important evidence to prove the validity of the capillary leakage hypothesis requires the demonstration that an adequate blood volume cannot be restored by replacement therapy Data with respect to this issue were lacking until improved methods for measuring blood volume became available As will be shown below the improved methods for blood volume determination indicate that adequate or more than adequate replacement of the blood volume lost does in fact restore a sufficient and a sustained blood volume even while the shock state is rapidly deteriorating (57) Although doubt *still exists that such methods are accurate in a state of failing* peripheral flow the evidence, as far as it goes is in conflict with the "capillary leakage hypothesis

The technique of the dye–plasma–hematocrit method depends on dilution of the dye by the total blood mass. Discrepancies between estimated and determined whole blood and plasma volumes in advanced shock have been shown to be due to inadequate mixing of the dye with the total blood mass within the time limits which suffice for this purpose in a normal circulation. Apparently false dilution curves are due to the sluggish state of the peripheral circulatory bed, the evidence for which though considerable has been amplified recently

The accuracy of this method for determination of total blood volume depends on its utilization of the hematocrit level of large vessel blood for measuring red cell volume. Gibson *et al.* (37) presented evidence "to prove beyond question that the red cell volume calculated from the determined plasma volume and the hematocrit of blood samples drawn from auricle arteries or veins is always higher than the true volume in the normal state This is because the hematocrit of that portion of the blood circulating through the minute vessels is about ½ that of the blood in large vessels. The hematocrit of all the blood in the body is always lower than the large vessel hematocrit. Thus the dye–plasma–hematocrit method gives values that are from 10–30 per cent too high." The error is even greater in advanced shock due to "the greater spread between auricular and minute vessel hematocrit Regardless of hemoconcentration or hemodilution, the magnitude of this spread is such that the error is consistently from 20–40 per cent too high so that significant changes in red cell volume may not be detected.

The weight of the testimony is that the conditions set forth above as essential to establish this theory do not conform to the facts Nevertheless, since a large and critical plasma loss, if uniformly distributed, may exist without producing overtly wet tissues, it was found necessary to subject the theory to experimental study by a quantitative determination of the amount and distribution of extravasated plasma in several varieties of shock.

The reader may find tedious the following discussion relating to capillary permeability which is given in considerable detail. But since the theory of capillary permeability continues to dominate the average reader's concept of shock, it appears necessary to give a reasonably full account of the evidence which contradicts it.

The approach to this problem required that a chemical label be attached to plasma proteins, so that they could be identified unmistakably after leaving the circulation and measured quantitatively

The capillary leakage hypothesis assumes that plasma (or some of its constituents) escapes from the general capillary bed at a greater than normal rate and that it fails to return to the circulation as fast as it leaves, resulting in a net gain of plasma to tissues outside of localized areas of injury

Radioactive sulfur was first selected for this purpose The reasons for this selection were (*1*) Sulfur occupies a relatively stable position in the protein molecule, and plasma protein made radioactive by incorporation of radioactive sulfur should be identical in chemical and biological properties with normal plasma protein (*2*) Whipple *et al.* (42a,69,90) have demonstrated the significant role which sulfur-containing amino acids play in the generation of plasma proteins. (*3*) The half life of radioactive sulfur is 88 days thus permitting radioactivity determinations over the period of time needed to carry out the experiment.

It was necessary first of all, to synthesize radioactive, sulfur containing amino acids (cysteine methionine, and homocystine) from radioactive sulfur (74) These were then fed to dogs which were made hypoproteinemic by Whipple's method When a total blood protein level of 4 Gm. per hundred cubic centimeters was reached, one radioactive amino acid, together with 50 grams of casein, was administered daily by stomach tube. In most cases *l*-tyrosine was added in a few *l* tryptophan. The low protein level was maintained by continued plasmapheresis and the removed plasma was collected and its radioactivity determined. It was found that radioactive

cysteine was incorporated in plasma protein far better than methionine or homocystine The radioactive plasma was prepared for use by dialysis to remove traces of radioactivity present in the non protein fraction. It was then injected as such, or after concentration, into normal control dogs and into dogs subjected to shock.

The migration of intravenously injected radioactive protein as *a means of tracing the movement of normal plasma protein between* the circulation and the tissues is valid only to the extent that such

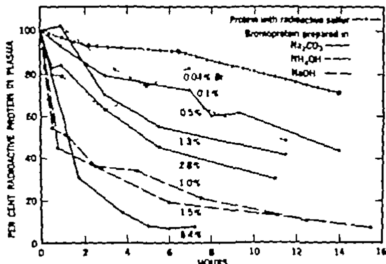


Fig 1 *Rate of disappearance of radioactive bromoprotein (containing various percentages of bromine and prepared in several ways) from the circulating plasma of normal anesthetized dogs, compared to radioactive plasma protein containing radioactive sulfur*[38]

radioactive proteins are not denatured. Denaturation of the protein must be minimal or avoided altogether lest the experiment be a measure of the escape of a foreign rather than normal plasma protein. The rate of escape of radioactive sulfoprotein from the blood of a normal anesthetized dog is shown in Figure 1 The curve of declining radioactivity of the circulating blood due to injected radioactive sulfoprotein shows that 90 per cent of the radioactive protein was circulating 5 hours after injection 70 per cent, 15 hours after injection and 45 per cent, 48 hours after injection. The rate thus determined at which injected radioactive sulfoprotein disappeared from the blood of normal dogs provided a curve showing the

rate of disappearance of normal plasma proteins This curve may be used as a standard for determining any change in rate in dogs subjected to shock, and for comparison with the disappearance rate of proteins tagged with other radioactive atoms which produce slight denaturation. This rate is roughly comparable to the rate at which Evans blue (T 1824) disappears from the circulation, since the dye is firmly attached to plasma proteins its disappearance also provides an index of the rate of migration of normal plasma proteins (64)

When the experiment was finished tissues were analyzed quantitatively for extravascular radioactivity in order to correlate the loss of radioactive protein from the blood with the gain in radioactive protein by the tissues This is necessary because the total plasma loss from radioprotein disappearance curves cannot be calculated unless the plasma volume is known with certainty Plasma volume measurements may not be precise when as in shock, areas of stagnation exist there may be incomplete mixing at the time of sampling, with a resulting inaccurate reading of the degree of dilution of an injected dye or tagged substance The independent determination of plasma loss by direct determination of the protein which has actually left the circulation serves as a check against the results of plasma volume determinations and at the same time provides a means of discovering whether or not the loss into tissues is distributed uniformly or preferentially

The extravascular content of plasma proteins per gram of tissue was determined by subtracting from the total radioactivity per gram of tissue the fraction due to intravascular plasma protein. The intravascular plasma protein content was determined from the hemoglobin content per gram of tissue and the estimated capillary hematocrit.

PLASMA LOSS IN HEMORRHAGIC SHOCK

The following is a summary of the procedures involved in obtaining the necessary data (25) Heparinized dogs were put into hemorrhagic shock by fractional bleeding to a blood pressure level of 70 mm. Hg. (Some dogs in earlier experiments received sodium barbital according to Wiggers' technic (91) all others received local anesthesia) The disappearance curve of radioactivity in *normal dogs* was found to be the same in both anesthetized and unanesthetized dogs In each experiment, comparable doses of radioactive plasma were given intravenously to a normal and shocked dog simulta

neously, some time before or immediately after the shocked dog had been bled. Thereafter interval sampling for radioactivity measurements was done in both dogs until the death of the shocked dog. The

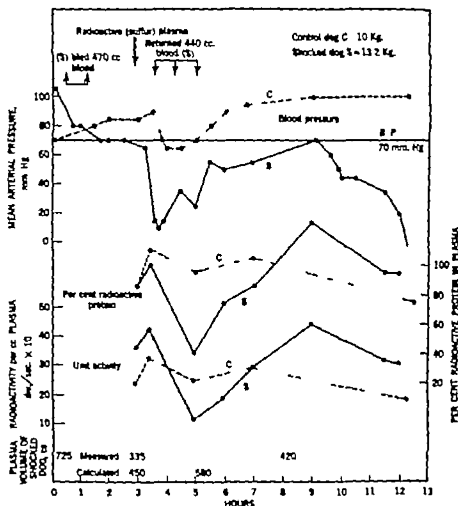


Fig. 2. Rate of disappearance of radioactive sulfoprotein in dog in hemorrhagic shock, compared to that in control dog.[26]

calculations of residual circulating radioactivity and unit of radioactivity (i.e., per cubic centimeter of plasma) for the normal and shocked dogs were made throughout the experiment with appropriate corrections for differing conditions between the two (25) The dog

in shock and the normal dog were killed by exsanguination in order to reduce the blood content in tissues. Tissue samples were taken from both dogs, and the total radioactivity per gram of tissue was then determined. The blood content of skin, bowel brain and omentum was so small that the correction required for the intra vascular component in these tissues was insignificant. Usually, the correction required for the blood content of liver, lung, and kidney was not inconsiderable.

Two experiments were performed with radiosulfoprotein. The dis appearance rate of this protein before and during the state of hemor rhagic shock compared closely enough with that in normal dogs to show that the rate of escape of plasma proteins was not noticeably altered in the shocked animal (Fig. 2)

For the experiments in Figure 2, radioactive plasma containing radioactive sulfur was used. Plasma volume determination in the shocked dog at the beginning of the experiment, and just before the terminal decline in blood pressure, showed a deficiency of nearly 300 cc. of actively circulating plasma, even though nearly all the blood had been returned.

The radioactivity curves show a rapid loss of radioactive protein during the period of rapid collapse, and mobilization of radioactive protein into the active circulation after transfusion and rise in blood pressure had occurred. No evidence of mobilization of radioactivity was noted in experiments in which the radioactive protein was given before hemorrhage, when adequate mixing with the circulating plasma was allowed. It is therefore possible that the observed phenomenon is due to inadequate mixing of radioactive plasma, rather than to loss through capillary leakage.

The plasma deficiency observed by the dye method is 37 per cent of the original volume. This is much higher than that observed in any other experi ment involving transfusion in the late shock phase, suggesting that the defi ciency in part at least, may have been due to poor mixing of dye. That inadequate mixing existed in this experiment was evident from the curve of radioactivity following injection of radioactive protein.

In another experiment, radioactive plasma containing radioactive sulfur was injected before hemorrhage. Both control and shock dogs suffered a nitritoid reaction, with a drop in blood pressure to 70 mm. Hg. During the succeeding 6 hours, both blood pressures returned to normal. The shocked dog was then bled and shock ensued for 3 hours, with a gradual decline of blood pressure to 45 mm. Hg. Blood withdrawal for plasma volume determination killed the shocked dog.

Six hours after the injection of radioactive plasma, the per cent of radioactive protein circulating in the plasma and the unit activity of plasma was about the same in both dogs. The slopes of the curves remained parallel during onset of shock in the shocked dog. These observations are similar to those noted with radioactive bromoprotein.

The difficulty of obtaining enough radioactive sulfur for a sufficient number of such experiments led to the use of radioactive bromine and later of radioactive iodine These elements can be coupled directly to form a stable linkage with plasma proteins (26) Their use enormously simplified the preparation of radioactive plasma proteins the disadvantage however is that they unavoidably dena

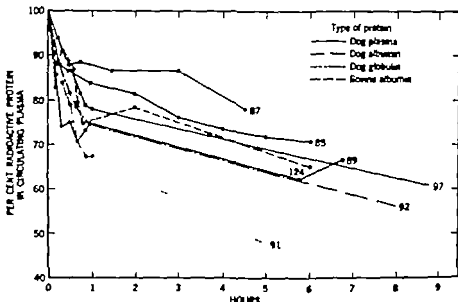


Fig. 3. Rate of disappearance of radioactive iodoprotein from the circulating plasma of normal dogs.[*] The number with each curve refers to the dog number The dog albumin contained some globulin. The dog globulin was precipitated by prolonged dialysis and was redissolved with the aid of sodium carbonate The bovine albumin was prepared from crystallized bovine albumin provided through the courtesy of Prof. E. J Cohn, Department of Physical Chemistry Harvard Medical School.

ture the protein. By controlling the reaction so as to permit the incorporation of approximately only one atom of halogen to one protein molecule denaturation was kept to a minimum. Halogenated proteins so prepared were dialyzed to remove all unbound halogen before use Test curves of disappearance of brominated and especially of iodinated protein were close enough to that of sulfoprotein to permit their use (Figs. 1 and 3)

In some 8 experiments on hemorrhagic shock, using the various radioproteins mentioned, the results were sufficiently uniform so that

there is no need to cite the results of more than one or two representative experiments

Experiment B 11 Three morphinized dogs—C (control), S_1 (to be bled into reversible shock), and S_2 (to be bled into irreversible

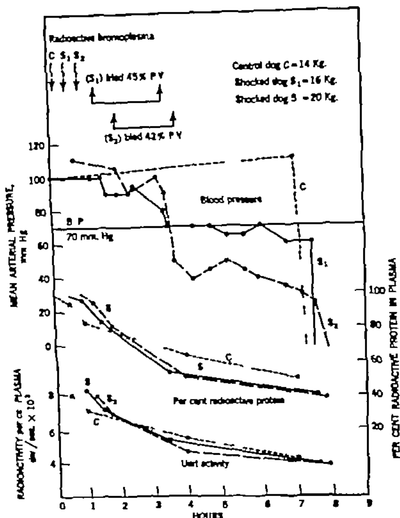


Fig. 4. Rate of disappearance of radioactive bromoprotein from the circulating plasma in shocked dogs, compared to that in control dog." The increased slope of both radioactivity curves for dogs S_1 and S_2, as compared to that of dog C, immediately after bleeding, is probably due to dilution by mobilized extravascular fluid. Their subsequent parallel course indicates that the shocked dogs did not lose radioactive protein from the plasma at a greater rate than the control dog. There is no difference in the disappearance curves between the dog in deep shock (S_2, probably irreversible) and the dog in less severe shock (S_1, probably reversible)

shock—were given radiobromo-plasma protein intravenously in proportion to their body weight. Dogs S_1 and S_2 were then bled into shock. The blood pressure was followed and blood samples were taken at varying intervals until dog S_2 died. At this time, dogs C and S_1 were exsanguinated and samples of different tissues from all three dogs were taken for analysis of intravascular and extravascular radiobromoprotein content. The disappearance of radiobromoprotein

TABLE I

Ratio of Tissue Radioactivity of Shocked Dogs to Control Dog (27)

Tissue	Ratio, dog S_1 to control dog, per cent	Ratio, dog S_2 to control dog, per cent
Liver	59	99
Lung	110	91
Kidney	183	125
Stomach	67	83
Ileum	66	68
Colon	67	56
Skin, thorax	216	225
Skin, back	130	110
Heart	130	135
Muscle foreleg	110	85
Muscle spinal	69	85

A ratio of 100 per cent indicates equal radioactivity per gram of tissue in control and shocked dogs. Less or more than 100 per cent signifies a lower or higher radioactivity per gram of tissue in the shocked dog. Ratios varying between 75 and 125 per cent are considered within the limits of experimental error in the experiments with radiobromoprotein.

from the blood is charted in Figure 4 in terms of (*a*) radioactivity per cubic centimeter of circulating plasma, and (*b*) total circulating radioactivity in per cent of the original amount injected. The latter is calculated as the product of the determined plasma volume and the unit radioactivity. The slope of both curves for dogs S_1 and S_2 immediately after bleeding shows an increase, as compared to dog C probably due to dilution by mobilization of extravascular fluid. But the subsequent parallel course of all three curves indicates that the dog in deep shock did not lose radioactive protein from the circulating blood plasma at a greater rate than the control dog, or the dog in moderate shock.

Analysis of the various tissues showed further that the extravascular plasma protein content of each tissue except that of the kidney

and skin of thorax, did not differ substantially among the three dogs (Table I) Furthermore, the calculated protein and plasma loss into the kidney and skin of thorax was not significant, quantitatively

With certain minor variations, similar results were obtained in most of the comparable experiments performed with radioiodoprotein.

The foregoing experiments provided no evidence of greater leakage of protein in irreversible shock than in reversible shock An increase in capillary permeability to protein that may have developed in the former might have been masked by the progressive diminution in

TABLE II

Ratio of Radioactivity (Radioiodoprotein) of Tissues of Dog in Irreversible Hemorrhagic Shock, as Compared to Control Dog in Reversible Hemorrhagic Shock, Including Plasma Loss in Whole Organs in Irreversibly Shocked Dog as Compared to Control Dog (26,27)

Tissue	Ratio, per cent	Plasma loss, cc.
Liver	13	0
Lung	32	0
Kidney	87	0
Intestine	68	0
Spleen.	112	1
Skin	41	0
Heart	62	0
Muscle	121	9.5
		Total 10.5

Ratios varying between 95 and 105 per cent are considered within the limits of experimental error in the experiments with radioiodoprotein. Any ratio below 95 or above 105, except in muscle, is taken to represent a difference outside of experimental error This error is much smaller than in the case of radiobromoprotein. The significance of such ratios is not evident in the ratio figures themselves, since two factors of importance affect the calculation. These are the relative weights of the organ and the relative radioactivity measurements of such organs per gram. For example, if a ratio of 200, derived from a radioactivity of 0 001 div per second on the electroscope in the control and a radioactivity of 0 002 div per second in the shocked dog, applies to a gram of tissue of a given organ (*A*) and the same ratio, derived from a radioactivity of 0.0001 div per second in the control and 0 0002 div per second in the shocked dog, applies to a gram of tissue of another organ (*B*) of the same weight, the difference in radioactivity per gram of tissue will be 0.001 for organ *A* and 0 0001 for organ *B* The total radioactive protein content of organ *A* will be ten times that of organ *B* and the quantitative loss involved is obviously far less in organ *B* even though the ratio is the same for both. The quantitative significance of an increased ratio is of little consequence in an organ like the kidney which is small in weight, and the same is true when a large organ has a very low order of radioactivity

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TABLE I

Ratio of Tissue Radioactivity of Shocked Dogs to Control Dog (2

Tissue	Ratio, dog S_1 to control dog, per cent	Ratio, d to contr per c
Liver	89	9
Lung	110	91
Kidney	165	12
Stomach	67	8
Ileum	66	6
Colon	67	6
Skin, thorax	215	23
Skin, back	120	116
Heart	130	13
Muscle foreleg	110	8
Muscle, spinal	80	8

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Spleen	112	1
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Muscle	121	9.5
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TABLE III

Ratio of Tissue Radioactivity of Shocked Dog to Control Dog (25)*

Tissue	Ratio (all values expressed in per cent)														Relative amts. of radioactivity in various tissues of 5 control dogs, per Gm.
	Expt. 13 ([illegible])		Expt. 11 ([illegible])		Expt. 11 ([illegible])		Expt. 7		Expt. 8B		Expt. 9		Expt. 8A		
	Act.	Corr.	Act.	Corr.	Act.	Corr.	Act.	Corr.	Act.	Corr.	Act.	Corr.	Act.	Corr.	
Liver	75	95	45	69	80	99	180	150	74	77	120	100	170	185	5.5
Lung	60	76	83	110	73	91	140	120	8	8.5	51	71	150	105	6.6
Kidney	68	86	140	185	100	125	105	140	39	41	77	110	120	130	8.5
Stomach			51	67	67	83									3.5
Ileum	53	67	50	60	55	68	250	210	85	89	90	125	91	99	4.1
Colon	37	47	51	67	45	56									3.5
Thyroid	90	115													3.1
Skin, thorax	66	83	185	215	190	235	49	42	51	53			140	150	2.3
Skin, back	64	81	100	130	87	110	67	57	83	86	100	220	210	230	2.0
Heart	100	125	100	130	110	135	190	100	70	82			95	100	3.2
Muscle foreleg	75	95	83	110	71	88	24	20	110	115	125	175	180	105	1.0
Muscle spine	53	67	68	80	71	88	51	43					85	93	1.3
Plasma	100		93		85		130		87		93		150		7.7
Correction factor		*128*		*151*		*124*		*85*		*104*		*180*		*109*	

The ratios are corrected for radioactivity of blood content of liver, lung, and kidney in experiments 13, 11, 9. Blood content of stomach, ileum, colon, skin, and muscle are too small to be significant. The "corrected" columns are calculated according to formulas given elsewhere. This correction is necessitated by differences between normal and shocked dogs in total and unit radioactivity of circulating plasma.

"Act." represents actual value.

capillary circulation, and might become manifest only if the capil laries were supplied with a sufficient volume of blood to favor fluid transfer Accordingly, experiments were carried out in which a transfusion was given to two shocked dogs when the shock in one had become irreversible. The following is a representative example.

Experiment I 7 Two dogs (nos 98 and 99) were bled into shock. After 7½ hours in shock, when his plood pressure was 20 mm. Hg dog 98 was given a transfusion of 470 cc of plasma containing radioiodoprotein. At the same time a transfusion of 345 cc of plasma containing radioiodoprotein was given to dog 99 which had been in shock for 3 hours, when his blood pressure was 30 mm. Hg. Dog 98 did not recover, when his blood pressure again declined to 25 mm. Hg the blood pressure of dog 99 who was recovering was 100 mm. Hg. Both dogs were exsanguinated simultaneously dog 98 yielding 70 cc and dog 99,230 cc of blood. Tissue samples for analysis were taken immediately from both with results shown in Table II, in which the ratio of radioactivity content per gram of tissue of dog 98 to that of dog 99 is given.

Except for muscle and spleen all the tissues of dog 98 contained less extravascular plasma than those of dog 99 There is accordingly no evidence of greater leakage of plasma in the dog in irreversible hemorrhagic shock, as compared to the dog in reversible shock, even after transfusion. On the contrary, the former probably because of a less efficient capillary circulation seems to have displayed a slower than normal rate of escape of iodoprotein from the circulation

From the data of all experiments (Table III) it may be stated that the radioactivity curves of the circulating plasma in normal and shocked dogs, including those which received infusions, are substantially the same. The disappearance of radioactive protein from the circulation, as judged by the curves of unit or residual radioactivity occurs at approximately the same rate in the shocked and in the normal dog receiving the same specimens of radioactive plasma. The unit radioactivity curves provide evidence as to whether or not a selective loss of protein or a shift in total water occurs in shock. The residual radioactive protein curves provide evidence as to whether or not whole plasma is lost in shock.

The continued fall in unit concentration of radioactivity without a simultaneous escape of whole plasma observed in all the unin fused control and shocked dogs studied signifies either dilution or

TABLE IV Plasma Volume in Hemorrhagic Shock (25)*

Experiment No.	Plasma withdrawn to produce shock, per cent	Plasma volume in shock (per cent)								Remarks
		First measurement				Second measurement				
		Duration of shock, hrs.	Expected	Found	Gain or loss	Duration of shock, hrs.	Expected	Found	Gain or loss	
1	46	1½	54	76	+22	4½	73	69	− 4	
2	46	1	54	67	+13					
3	63	1	37	55	+18					
4	60	1½	40	60	+20	4½	55	57	+ 2	
5	71	3	29	54	+24					Bleeding continued during shock
6	35	3	65	46	−19					
7	36	3	61	61	0					
8	45	½	55	63	+ 8	3	56	56	0	
9	44	2½	56	72	+16					
10	28	3½	72	66	− 6	4½	63	66	+ 3	
11	45	1	55	65	+10					
12	39	10	61	65	+ 4					
13	31	6	66	64	− 2					
14	61	5½	39	75	+36					
15	40	2½	60	81	+21	4	61	65	+ 4	
16	25	1½	75	96	+21	3	85	85	0	
17	20	1	80	84	+ 4					
18	42	3	58	78	+20	4½	71	75	+ 4	
19	58	4	42	51	+ 9					
20	36	2½	64	53	−11	5	85	78	− 0	2nd reading 1½ hrs. after blood transfusion
21	42	2½	58	64	+ 6	7	106	90	−16	2nd reading 3 hrs. after blood transfusion. Recovered.
23	15	1	85	70	−15	2	123	98	−25	2nd reading ¾ hr after plasma transfusion.
23	42	3½	58	58	0	4	97	87	−10	2nd reading ½ hr after plasma transfusion
24	68	2	32	59	+27	2½	119	85	−34	2nd reading ½ hr after 500 cc. saline infusion

All dogs died except as noted. * Average +9.3

escape of radioactive protein from the circulation Continuous dilution does not occur in the normal dog. While there is evidence of fluid mobilization early in shock, this is certainly not true later on. Since the unit activity fell at the same rate in the normal and in the shocked dogs, the equal loss of radioactive protein in both therefore signifies that the normal mechanism for the escape of such protein from the circulation was operating in both and was not due to dilution from mobilized fluid.

The tissue data were considered as representing the loss of whole plasma from the circulation. The loss of circulating protein without concomitant loss of the equivalent nonprotein fraction, or vice versa, would cause a shift in the plasma protein concentration. In traumatic shock the plasma protein concentration does not rise unless there is severe dehydration. It falls slightly in the early phase of shock because fluid is drawn from the tissues in response to the fall in blood volume. This fluid mobilization is limited in degree and duration, and does not occur in the late phase of shock when these determinations are made.

A quantitative estimate of the plasma loss into tissues cannot be made accurately because the unit activity of the lost plasma is not precisely known. Nevertheless the data as a whole indicate that such loss is small, that it involves only one or two tissues, which vary from one experiment to another and that it is probably not quantitatively significant except when infusions are given in the late phase of shock. Indeed, the frequency with which one observes a substantially smaller content of radioactive plasma in the tissue of the shocked dog, as compared to the control dog, suggests that the reverse may be true—less plasma may move out of the circulation in the shocked dog, presumably because of the contracted volume and decreased velocity of flow in the general capillary bed (see below)

Evidence that plasma does not escape from the general capillary bed in untreated shocked dogs also appears in plasma volume measurements in 24 dogs in hemorrhagic shock (Table IV) These showed an average gain of 9 per cent above the expected amount, during an early phase of shock as a result of mobilization of extravascular fluid. In 12 of these experiments plasma volume was measured again after a subsequent interval of shock. In 7 of these, no therapy was given and the volume was substantially unchanged. The remaining

5 received a saline plasma or blood transfusion in the late shock phase, with an average volume 19 per cent below what was expected from the volume of the infusion added to the volume previously determined The discrepancy between the expected and determined volumes might have been due to loss into the tissues (particularly in the case of saline infusion) but it might also have been due to increasingly inadequate mixing of dye with capillary blood. If in the late shock phase the peripheral blood is not in active circulation (in the same sense as the peripheral waters of a swamp with a brook running through its center are not in active circulation) complete mixing may not occur in the time interval allowed (15–30 minutes) The time required for complete mixing is not known when mixing is incomplete the insufficiently diluted dye results in a plasma volume determination which is too low False values, which would be most likely in late shock, would therefore overestimate plasma loss Since our figures are already in favor of no loss error in the method would only lend further support to our conclusion. The results with respect to plasma loss obtained by the dye volume method therefore are in line with those obtained by the radioactive protein technic Noble and Gregersen (57) came to the same conclusion from dilution curves obtained in clinical shock.

It is widely held that saline and other fluid infusions are responsible for washing protein out of the circulation The following experiment illustrates the method of inquiry regarding this concept.

Experiment I 9 Two dogs (nos 122 and 123) were bled into shock by a hemorrhage of 3.8 per cent and 4.0 per cent of their body weights respectively After 5 hours in shock when his blood pressure was 30 mm. Hg, dog 122 was given a transfusion of all shed blood containing 20 ml of bovine radioiodoalbumin, with a pressor response to 90 mm Hg When the blood pressure was 46 mm. Hg 4 hours later and the dog was in "irreversible" shock, an infusion of 1,500 cc of physiologic saline solution was given. This resulted in a maximum rise in blood pressure to 95 mm. Hg, with a subsequent decline to 60 mm Hg after another 3½ hours The dog was then exsanguinated (500 ml) All tissues were edematous and there were slight hemorrhages in the jejunum and colon

Dog 123, after 2 hours in shock with a blood pressure of 65 mm. Hg, received all shed blood containing 20 ml of bovine radioiodoalbumin. When the blood pressure was 100 mm. Hg, 4 hours later and the dog was in reversible shock 2,000 cc of physiologic saline

solution was infused The blood pressure rose to 140 mm. Hg, 3½ hours later, when it was 90 mm. Hg the dog was exsanguinated (600 ml.) All tissues were edematous, and there were slight hemorrhages in the jejunum

As a further control for comparison, a normal dog (no 124) was given 24 ml. of bovine radioiodoalbumin, 4 hours later, 1,500 ml. of physiologic saline solution were infused, and 3½ hours later the dog was exsanguinated (1,150 ml.)

TABLE V (26)

Plasma Loss in Whole Organs in Shocked Dogs (Irreversible and Reversible) as Compared to Normal Control Dog, Following Transfusion and Saline Infusion

Tissue	Plasma loss, ml.	
	Irreversible, dog [illegible]	Reversible, dog [illegible]
Liver	23	49
Lung	33	2
Kidney	10	0
Intestine	27	41
Spleen	3	0
Skin.	4	4
Heart	0	0
Muscle	140	0
Total	*240*	*96*

Radioiodoalbumin was given in proportion to body weight in all but the control dog. Correction for this was made in the final calculations

The hemorrhagic jejunum of dog 123 was analyzed separately for plasma content per gram, and found to be about the same as for the rest of the intestine in terms of total radioactivity, and less on the basis of extravascular radioactivity

If the calculated final total plasma volumes of these 3 dogs (all of whom received equivalent saline infusions) are taken to equal 10 per cent of their respective body weights minus the blood removed plus the volumes of blood and saline infusions the tissue radioactivity data show that in the irreversibly shocked dog the loss in plasma volume was 10 per cent greater than in the normal dog, while in the reversibly shocked dog it was 3 per cent greater than in the normal dog (Table V) One may conclude, therefore that saline

TABLE VI Protocol Data in Tourniquet Shock and Burn Shock and Comparison of Plasma Loss into Injured Extremity by Three Criteria (26)

	...*	Dog weight, kg.	$\frac{W^s}{W^c} \times \frac{I^c}{I^s}$	Duration of tourniquet (hrs.) or burn (sec.)	Duration of experiment after removal of tourniquet or burn, hrs.	Blood pressure at end of experiment, mm. Hg	Vol. ... of exsanguination at end of experiment, ml.	Hematocrit increase, per cent	Decrease in plasma vol. ... by dye method, ml.†	Weight increase of injured extremity Gm.	Plasma loss int injured extremities by radioactivity analysis of tissue, ml.	Remarks
Tourniquet Shock												
	84	8 7	1 0	5	5 7	75	270	8	300		102	Tourniquet on both hind legs
	85	6 0		Control		110	100	0				
I 2B	86	10 6	0 93	8	4 0	0	0	13	307		132	Tourniquet on both hind legs
	87	5 1		Control		110	200	0				
I-3	88	11 8	0 92	10 5	5 7	10	30	16	257	360	122	
				Control		120	500	0				
			[illegible]0	7 5	11 5	30	100	4	220	435	180	After 7 hours, increase in hematocrit was 13 per cent (dog 90)
				Control		105	150	0				
Burn Shock												
		8 5	0 93	45	27	0	0	1	45	121	100	Burn of foreleg and hind leg, blood pressure remained at 80 mm. Hg, dropped to 30 mm. Hg after small dose of nembutal (dog 91)
		5 0		Control		110	200	0				
		6	1 0	90	18 5	0	0	16	230		415	Burn of both hind legs
				Control		110	480	2				
			[illegible]0	120	23	30	0	8	785	60	21	Plasma infusion (325 ml.) with radioprotein
				20	21	95	150	11	2[illegible]0	171	39‡	Plasma infusion (270 ml.) with radioprotein

* ...re ...ative proportion of radioprotein dosage to weight of shocked versus control dog, when W = weight of dog, I = volume of ...ve plasma injected, c = control dog, and s = shocked dog. † In burn experiments, plasma volumes by dye method were complicated ...mar...ed hemolysis. ‡ Since tagged infusion was given 4½ hours before end of experiment, loss during this period only was determined.

infusion increases the leakage of plasma protein in shock, and more markedly in irreversible shock. The tissues showing most significant leakage were muscle, intestine, lung, and liver However, it is unlikely that the loss of 10 per cent of the plasma volume after the large saline infusion in the irreversibly shocked dog was responsible for the subsequent decline in blood pressure

The foregoing evidence demonstrates that no significant volume of plasma is lost from the vascular bed as a result of the existence of a state of hemorrhagic shock. The progressive nature of the disorder does not arise from an *increasing* imbalance in the proportion of blood volume to extravascular fluid volume. While the integrity of the capillaries may be impaired in the late shock phase, an increase in capillary permeability if present, is not a factor in the fatal issue. The conclusion follows that death in hemorrhagic shock is not due to a progressive decline in plasma volume following the initial loss of blood volume.

PLASMA LOSS IN TOURNIQUET AND BURN SHOCK

Since the forces operating to produce lethal shock are not necessarily the same in all types of shock, it was necessary to obtain data on the question of generalized increase in capillary permeability in conditions other than hemorrhage Tourniquet shock and burn shock differ from hemorrhagic shock in that (*1*) a local loss into areas of injury occurs and (*2*) such injured tissues perhaps may liberate a substance capable of affecting capillary permeability in general.

Tourniquet shock was produced in morphinized dogs by applying 5 to 6 turns of heavy walled rubber tubing as high on the leg as possible, as tightly as possible and held with a screw clamp Previous investigators, who employed barbiturate anesthesia, produced fatal shock if a tourniquet was applied for 5 hours In our experiments, in which barbiturates were not used fatal shock did not occur unless the tourniquet was left on for at least 8 to 9 hours. Radioactive protein was injected 30 minutes before the tourniquet was removed.

Burns were produced under ether anesthesia in morphinized dogs by immersion of 1 or 2 extremities in hot water (98 C.) for varying periods of time. In contrast to the observations of others who used barbiturate anesthesia (14) we did not produce fatal shock by im mersion in water at 98 C for 20 seconds.

In one experiment (1-4, Table VI) immersion of 2 legs in water at 98 C. for 45 seconds did not produce fatal shock, but administration of a small amount of nembutal intraperitoneally 24 hours later produced a drop in blood pressure to 30 mm. Hg, followed by death.

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Experiment No.	Dog No.	Dog weight, kg.	$\frac{W}{W_c} \times \frac{I}{I}$	Duration of tourniquet (hrs.) or burn (sec.)	Duration of experiment after removal of tourniquet or burn, hrs.	Blood pressure at end of experiment, mm. Hg	Volume of ex sanguination at end of experiment, ml.	Hematocrit increase, per cent	Decrease in plasma vol. ... by dye method, ml.†	Weight increase of injured extremity Gm.	Plasma loss into injured extremities by radioactivity analysis of tissue, ml.	Remarks
						Tourniquet Shock						
I 2A	81	8 7	1 0	5	5 7	75	270	8	300		102	Tourniquet on both hind legs
	85	6 9		Control		110	100	0				
I 2B	86	10 6	0 93	8	4 0	0	0	13	307		132	*Tourniquet on both hind legs*
	87	5 1		Control		110	200	0				
I-3	88	11 8	0 92	10 5	5 7	10	30	16	257	300	122	
	89	14 1		Control		120	500	0				
I-4	90	13 4	1 0	7 5	11 5	30	100	4	220	435	180	After 7 hours, increase in hematocrit was 13 per cent (dog 90)
	92	8 2		Control		105	150	0				
						Burn Shock						
I-5	91	8 5	0 93	45	27	0	0	1	45	121	100	Burn of foreleg and hind leg; blood pressure remained at 80 mm. Hg, dropped to 30 mm. Hg after small dose of nembutal (dog 94)
	95	5 0		Control		110	200	0				
I-6	96	11 6	1 0	90	18 5	0	0	16	230		445	Burn of both hind legs
	97	10 6		Control		110	480	2				
I-8	200	11 8	1 0	120	22	30	0	8	785	60	24	Plasma infusion (325 ml.) with radioprotein
	201	10 1		20	21	95	150	11	230	171	39*	Plasma infusion (270 ml.) with radioprotein

Formula shows relative proportion of radioprotein dosage to weight of shocked versus control dog, when W = weight of dog, I = volume of radioactive plasma injected, c = control dog, and s = shocked dog. * In burn experiments, plasma volumes by dye method were complicated by marked hemolysis. Since tagged infusion was given 4½ hours before end of experiment, loss during this period only was determined. †

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In one experiment (1-4, Table VI) immersion of 2 legs in water at 98 C. for 45 seconds did not produce fatal shock, but administration of a small amount of nembutal intraperitoneally 24 hours later produced a drop in blood pressure to 30 mm. Hg, followed by death.

For this reason, burns for longer periods of time were used In such cases marked hemoglobinemia was produced In one experiment (I-8) a dog receiving a nonfatal burn was used as a control for a dog with fatal burn shock. Radioactive protein was injected 30 minutes before the animal was burned (except in experiment I-8)

Tourniquet Shock

Tourniquets were applied at the groin to one or both legs of a dog under morphine (3 mg./kg.) and left on for 5 to 10 hours. Plasma volume was then measured and radioiodoprotein was given to this dog and to a normal morphinized dog in equivalent amounts. The tourniquet was removed, and the same measurements were made as in experiment I 7 Table VI lists the results of tissue analyses of 4 dogs (I 2A I 2B I-3 and I-4) showing plasma protein loss in various tissues including the tourniqueted extremities. While the results indicate loss of protein into some tissues other than those of the extremities such loss involves only one to three tissues and in no case is the total loss outside of the extremities quantitatively significant from the point of view of plasma protein depletion. There is therefore no evidence that a change in permeability to proteins outside the area of injury if it exists is of consequence in the development and progression of shock following the removal of a tourniquet.

The volume of plasma loss into the tourniqueted extremities is of course large. The gain in weight was not determinable in experiments I 2A and I 2B where both legs were injured, but in experiments I-3 and I-4 the weight increase (above the normal leg) was much greater than the plasma gain determined by radioactivity assay of the tissues or the plasma loss from the circulation determined by the dye technic. The discrepancy is far in excess of errors in method and the difference, therefore largely represents a gain in tissue water drawn from outside areas

Burn Shock

Three experiments were performed in which one or more extremities were immersed in water at 98 C under ether anesthesia for varying intervals (Table VI) In experiments I-5 and I-6 radioiodoprotein was injected intravenously into a normal dog and into

the burned dog before the burn was produced In experiment I-8, the technic was varied in order to see whether the capillaries were more permeable to protein in a severely burned than in a mildly burned animal. For this purpose, 2 dogs were burned, one for 120 seconds, the other for 20 seconds. Four hours before the death of the more severely burned dog, a plasma infusion containing radioiodoprotein was given simultaneously to both dogs

The extravascular radioactive protein content of the tissues in all three experiments showed that the unburned tissues of the burned dog contained virtually no more plasma protein than the same tissues in the unburned control dog (experiments I 5 and I-6) or the less severely burned control dog (experiment I 8) The plasma protein loss outside the areas of injury involves only one or two tissues, which vary from one experiment to another, and in any case is not quantitatively significant.

In experiment I-8, the radioactive protein was injected too late to permit a determination of total plasma protein loss into the burned area. In the severely burned dog, the very small increase in weight of the burned extremity suggests that peripheral vascular collapse was due in large part at least, to factors other than plasma volume deficiency

The rise in total blood protein concentration in burn shock and in tourniquet shock (14) may reflect a disproportionate loss of the nonprotein fraction of plasma or a loss of extracellular fluid as well as of plasma into the injured area. A loss of the nonprotein fraction into tissues outside the injured area is not likely without a loss of a measurable amount of protein. Since no protein is lost into such areas it appears that no plasma is lost outside of areas of local injury The results indicate rather that water is drawn from outside areas and lost into the injured areas in other words uninjured areas are dehydrated.

The evidence provided above contradicts the theory of a general ized increase in capillary permeability in three varieties of advanced shock. This evidence is sustained by the experiments of Fink *et al.* (28) who studied the question of capillary permeability in shock due to trauma by a method similar to the one described above. Lysine, labelled with heavy nitrogen was incorporated in the plasma protein of dogs Such proteins, which can be regarded as not denatured when injected into the circulation of normal dogs, were found

to disappear at a rate very close to that of radiosulf plasma proteins In dogs in traumatic shock from intestinal trauma or muscle crush injury this rate was not altered If anything, the rate of escape was a little slower in the dog in shock than in the normal dog

Hemodynamics of Shock

The circulatory collapse following adequate volume replacement therapy in advanced traumatic shock is accompanied by a decline in the effective circulating volume, despite the infusion of fluids which do not leave the circulation. The search for the cause of irreversibility therefore, requires a more critical analysis of the hemodynamics of shock than has been made heretofore.

This aspect of the problem has received intensive but not exhaustive study in the past few decades. Until recently the exact state of affairs in the arteriolar capillary and venular beds was not precisely known. Nor were the effects of changes in the physical or chemical structure of the blood on the general circulation well defined. Functional alterations of the kidney intestines, heart and liver, and the intermediary metabolism of proteins and carbohydrates, in response to the anoxia and ischemia of shock have recently come under closer scrutiny These will be examined in a later section of this paper At this juncture, we shall deal with recent experimental findings within the circulation, especially with reference to peripheral flow and cardiac output and the effect of viscosity changes on both.

Chambers and collaborators (12a–b) made microscopic observations on the capillary flow in the rat s mesentery in hemorrhagic shock. They were able to show a progressive deficiency in peripheral flow The sequence of events as shock progressed in the various components of the peripheral circulation was described as follows Following an initial large hemorrhage, equivalent to 3 to 3.5 per cent of body weight, the larger arteries and veins constrict an increase in frequency and amplitude of vasomotion (alternate contraction and dilatation) of the arterioles and precapillaries appears and the normal constrictor response of these vessels to epinephrine is increased This they termed the "hyperreactive phase. After the hypotension is maintained for some hours by graded hemorrhage a pronounced slowing of flow occurs the venules dilate vasocon

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striction lessens and epinephrine sensitivity decreases. This they termed the "hyporeactive phase." During the hyperreactive phase, the capillaries are relatively ischemic and much of the blood is shunted through more direct arteriovenous communicating channels. After the hyporeactive phase continues unrelieved for some hours, the precapillaries lose their sphincteric action, with a resulting sluggish flow and finally stagnation of red cells in the capillaries and dilated atonic venules, while the bulk of the much reduced effective circulating volume continues to by pass the capillaries through arteriovenous communications. According to these authors the large vessels remain constricted until death, although Page and Abell (59) observed terminal vasodilatation. The final phase—pooling of blood in capillaries—results not only from loss of muscle tone in the arterioles and precapillaries, but also from loss of sufficient pressure to sweep the blood forward into the veins. Many capillaries are therefore virtually out of circulation. The phenomena of the hyporeactive phase are evidence of a failing circulation, and are a function of the duration rather than of the degree of hypotension.

Fine, Frank, and Seligman (24a) observed peripheral flow in the dog's exteriorized omentum in response to various therapeutic procedures and confirmed these findings.

Since these observations, which pertain to the portal circulation, may not reflect the state of affairs in the general capillary bed further evidence in regard to the peripheral circulatory bed is needed. Generalized anoxemia in shock is readily demonstrable from the observed, universally low oxygen tension in venous blood. A corresponding degree of tissue anoxia need not exist if more complete extraction of oxygen from the blood is being achieved. If however it can be shown that the capillaries are more or less out of contact with the active blood stream, the existence of tissue anoxia can be safely inferred. That this is the case is shown by the following evidence (27,33,37)

(*1*) The fall in pH of the venous blood exceeds that of the arterial blood as hemorrhagic shock progresses. The fall in carbon dioxide content in response to hyperventilation is considerably less in the venous blood than in the arterial blood. These findings point to the existence of a decreasing velocity of peripheral flow because the induction by a saline infusion, of a transient increase in peripheral flow as observed in omental capillaries, runs parallel to a transient

reversal toward normal of the pH and carbon dioxide and venous oxygen concentration values.

(2) Of 15 dogs in hemorrhagic shock breathing oxygen at 3 atmospheres, 7 showed a sustained normal or better than normal venous oxygen concentration without a noticeable beneficial effect upon the course of the shock state (33) Such an apparently futile correction of oxygen values presumably can be achieved only by a transfer of oxygen through arteriovenous shunts to the virtual exclusion of a sluggish capillary bed.

(3) That some capillary blood is out of contact with the active circulation, and that the latter traverses a shortened circuit was demonstrated as follows Morphinized dogs were given an intravenous dose of red cells containing radioactive iron (47 day half life) and the red cell volume was determined by the dilation principle used for plasma volume by the dye method. The plasma volume was also measured at the same time. Bleeding into shock was then performed and after some hours in shock an additional dose of radioactive red cells was given. In a number of experiments, the resulting increase in radioactivity per cubic centimeter of cells was more than the expected amount indicating dilution of the radioactive red cells by a red cell volume which was less than expected after allowing for the volume removed by bleeding. This is regarded as evidence that all red cells in the circulation fail to mix with the second dose of radioactive red cells and that stagnation of red cells exists somewhere in the peripheral bed

Further evidence of stagnation ("trapping") was obtained as follows Dogs in hemorrhagic shock received a dose of radioactive red cells Upon death of the dog the number of red cells in cubic centimeters per gram of tissue was determined by two formulas

$$(A) \quad \frac{\text{Hb in 1 gram tissue}}{\text{Hb in 1 cc. arterial blood (just before death)}} \times \begin{matrix}\text{arterial}\\ \text{hematocrit}\end{matrix}$$

$$(B) \quad \frac{\text{radioactivity } (Fe^{*})\text{/gram tissue}}{\text{radioactivity } (Fe^{*})\text{/1 cc arterial blood (just before death)}} \times \begin{matrix}\text{arterial}\\ \text{hematocrit}\end{matrix}$$

Formula *A* determines the *total* number of red cells in cubic centimeters per gram of tissue while formula *B* determines the number of red cells in cubic centimeters per gram of tissue in sufficiently

active circulation to have reached the tissue from the time of injection of radioactive red cells until death The discrepancy between the results of the two formulas is a measure of the incompleteness of the mixing and therefore to what extent blood has been trapped out of active circulation. The average ratio of formula *B* to *A* was found to be 1 ± 0 1 in 9 normal morphinized dogs The average ratio in the shocked dogs was 0 7 to 0.8, indicating that some 20 to 30 per cent of the red cell volume in tissues was trapped in the peripheral bed i e., by passed by the active stream.

Such a degree of trapping could not be demonstrated with equal uniformity for plasma This may possibly be due to a partial balancing of trapped plasma by mobilized extravascular fluid It may also be that in shock the mixing of plasma in active circulation with that in the peripheral bed is physically easier than is the case for particulate material such as red cells The latter hypothesis is thought not to be true for the normal dog, according to Hahn *et al.* (42)

As shock deepens the trapping may be expected to increase. In later experiments the technic adopted for measuring the volume of trapped blood was altered in order to avoid errors (see below) inherent in hemoglobin measurements for determination of red cell content. A dose of radioactive red cells with a 5 year half life was injected in the dog before inducing hemorrhagic shock. After shock had reached an advanced stage, a dose of radioactive red cells with a 47 day half life was injected.

Prof. Robley Evans and co-workers, of the Massachusetts Institute of Technology constructed Geiger counters which are capable of distinguishing between and accurately determining the radioactivity of the two types of iron in the same blood or tissue sample.

If trapping exists, the radioactive red cells with a 47 day half life should be incompletely diluted, in proportion to the degree of trapping, allowing for the red cells removed by bleeding in the calculation. Analyses of the tissues for the two types of radioactive iron permits two separate calculations of the number of red cells in cubic centimeters per gram of tissue The two determinations of red cell content may be expected to agree if complete mixing occurs when both types of radioactive red cells are injected If stagnation is present when the second dose (47 day half life radioactive iron) is injected, the cubic centimeters of red cells per gram of tissue calculated on the basis of 47 day half life radioactive iron should be less

in proportion to the degree of stagnation. This was found to be the case.

On an average the tissue content of 47 day half life iron was some 80 per cent of that of 5 year half life iron. This agreed with the observation that dilution of the second dose of radioactive red cells was approximately 80 per cent of the expected amount. The conclusion follows that some 20 per cent of the red cell volume is relatively stagnant in the peripheral bed in advanced hemorrhagic shock.

Experiment I-8 (Table VI) illustrates an extreme degree of segregation of blood in the peripheral bed in the case of a severe burn inflicted on one hind leg of a dog weighing 11.8 kg. 22 hours later the dog was in deep shock but the hind leg had gained only 69 grams in weight. The original plasma volume was about 600 cc., and 325 cc of plasma had been infused. By the dye–plasma volume method a subsequent decrease or "loss" of 785 cc in plasma volume was measured. This value may be too high due to marked hemolysis from the burn. However since little loss occurred into the leg, as indicated by the small weight gain and a rise of only 8 per cent in hematocrit, the loss indicated by the dye–plasma volume method was that out of active circulation but not from the capillary bed.

The foregoing data demonstrate that shock is a state in which a decline in effective circulating plasma volume exists as a result of partial exclusion of and stagnation in the capillary bed and that tissue anoxia necessarily results.

The total blood volume is usually deficient in shock but this is not always so. In shock resulting from severe infection, a deficiency in blood volume may not be present. Thus Ebert and Stead (21) could find no deficiency in the plasma volume of 8 patients in shock as a result of severe infection Freedberg *et al* (30) observed an extreme degree of shock from dysentery or diphtheria toxin but the fall in blood volume was quantitatively much less than is lost when shock results from hemorrhage or trauma

Since shock can exist in the absence of a demonstrable or significant fall in plasma volume or in spite of replacement of a known deficiency and since the replaced plasma does not leave the circulatory bed the essential defects in irreversible hemorrhagic shock even when the blood volume equals or exceeds that present before shock occurred are first, inefficient circulatory distribution of the total blood volume and second inadequate velocity of flow through capillaries

There is no valid evidence to show that the peripheral circulation in other types of shock differs essentially from that in hemorrhagic shock. Although Chambers *et al* (12a, 12b) observed a greater pooling in tourniquet shock than in hemorrhagic shock, the essential characteristics of the collapse of the peripheral vascular mechanism were the same in both Moreover this stagnation is a generalized phenomenon and is not confined to damaged tissues, since it exists in shock due to simple blood letting, in shock caused by a nonlocal lung infection, and in tissues distant from the site of injury in burn shock and in muscle crush injury

It has been repeatedly asserted that there is a difference in flow favoring the splanchnic bed at the expense of other areas. The greatly reduced venous oxygen concentration in portal blood, the damage inflicted on liver function (23a–b,71) and on the absorptive capacity of the small intestine (38) and the observed failure of the circulation in the exteriorized omentum reflecting in all respects the events which all agreed are happening to the circulation elsewhere, does not support this contention. If "congestion" of the liver and intestine seen at postmortem examination is to be taken as support ing evidence, the "congestion of the kidneys and lungs which is also present, would compel their inclusion in the fields of preferen tial flow The early and severe suppression of renal function (19 47,62 76) is not in harmony with an interpretation of "congestion" as being equivalent to increased flow On the contrary, congestion in such organs is better explained by the phenomenon of pooling or stagnation. The extent of the decline in effective circulating volume may be regarded as an indirect measure of the degree of such congestion, in view of the well known fact that exsanguina tion of the dog in advanced shock yields a much smaller proportion of the total blood volume than exsanguination of an unshocked dog.

Peripheral stagnation explains the fact that the administration of whole blood or plasma in advanced shock is frequently of no endur ing value. Since these fluids do not escape from the circulation, except in limited degree into areas of injury, it is obvious that when infused fluids fail to restore the circulation they accumulate in already sluggish or stagnant reservoirs (the capillary and venous bed) and probably only serve to embarrass the circulation still further particularly if given in excessive volume. Peripheral vascular congestion" in these circumstances is produced or aggravated because of a therapeutic plethora.

TABLE VII

Average Volume of Red Cells per Gram of Tissue of Various Organs in Normal and Shocked Dogs, as Established by Hemoglobin and Radioactive Iron Determinations (27,37)

Tissue	Hemoglobin					Radioactive iron	
	Normal, cc.	Normal exsanguinated, cc.	Hemorrhagic shock, cc.	Tourniquet, cc.[b]	Burn shock, cc.[b]	Normal, cc.	Hemorrhagic shock, cc.
Liver	0.050	0.011	0.054	0.037	0.043	0.058	0.021
Lung	0.073	0.038	0.095	0.038	0.071	0.079	0.052
Kidney	0.055	0.019	0.035	0.036	0.054	0.017	0.024
Intestine	0.0082	0.0016	0.017	0.006	0.005	0.011	0.0033
Spleen	0.188	0.021	0.050	0.060	0.120	0.30	0.007
Skin	0.0022	0.00090	0.003	0.002	0.001	0.0065	—
Heart	0.0091	0.0015	0.017	0.005	0.004	0.018	0.0052
Muscle	0.012	0.0050	0.021	0.003	0.005	0.0002	0.000
Injured extremity	—	—	—	0.003	0.019	—	—
Number of dogs	7	7	8	5	4	5	1

2 dogs killed by intravenous injection of nembutal or cyanide.

[b] 2 dogs received infusions of blood 3, of plasma 1 of saline and 3 were exsanguinated.

Does "congestion" in the absence of fluid therapy represent a quantitatively significant increase in the amount of blood in the peripheral circulation? Some objective quantitative data have recently been adduced on this question.

Weighed amounts of various tissues from normal and shocked dogs were taken immediately after death following exsanguination or intravenous administration of nembutal or potassium cyanide. The blood in the large vessels or on the surface of tissue samples was gently wiped away so that only the blood in the smallest vessels was left in the tissue A number of representative pieces from each organ or tissue such as lung, liver bowel, skin and muscle were pooled and aliquots taken for analysis The tissues were finely minced, extracted with distilled water at 40 C for 24 to 36 hours and filtered through gauze.

Myoglobin of heart and skeletal muscle was first extracted with saline solution, and the residue after centrifugation, was extracted with distilled water

The hemoglobin in the filtrate was measured after clearing with ammonia in a photoelectric colorimeter against standards from arterial blood (taken at the time of death) using filters 620 and 540 to correct for turbidity No correction for methemoglobin was made. Although inaccuracies in the hemoglobin measurement are unavoidable, the red cell volume in cubic centimeters per gram of tissue determined by this method agreed well enough with simultaneous red cell content determinations made by the radioiron red cell technic to permit our results to be accepted as a fair approximation of the facts. From the hemoglobin value, the red cell content per gram of tissue was calculated from formula *A* (page 26)) The liver lung kidney and spleen are the only organs containing appreciable amounts of red cells per gram. When the number of red cells per gram of tissue in dogs in untreated shock is compared to that of the normal dog, there is seldom more and usually less in the dog in shock (Table VII) except in the liver lung, kidney and spleen (26)

The acutely exsanguinated normal dog shows fewer red cells per gram of tissue than the nonexsanguinated normal dog or the dog shocked by hemorrhage.

Prinzmetal (65 66) has demonstrated a considerable increase above normal in the red cell content of the kidney and heart of the

rat in shock from burns The observation that certain organs contain more blood than other organs and tissues and occasionally somewhat more than their normal amount, is consistent with this finding. However it would be hazardous to conclude that the redistribution of the total blood mass represented by such "congested" tissues is a key factor in the fundamental disorder The peripheral circulation as a whole may be expected to contain more than its normal complement of blood if blood or plasma is infused but not if the total blood volume remains below normal.

The relative congestion of kidney liver, lungs and heart is doubtless due to a loss of tone in the peripheral circulation. This loss of tone Prinzmetal describes by the term "capillary atony" The microscopic observations of Chambers *et al.* (12a–b) show that the normal filling of capillaries is a completely passive one and is dependent upon the tone of the musculature in the precapillary sphincters and metarterioles If the capillaries normally are passive recipients of the blood delivered to them it is more appropriate in shock, to speak of arteriolar atony Decline in bleeding volume of the shocked animal is thereby readily explained "Decline in effective circulating volume" in excess of what is lost into an area of injury is another expression of the same phenomenon. With the progressive increase in arteriolar atony there is a further reduction of the already reduced cardiac output with death ensuing shortly thereafter in much the same way that a small bleeding during advanced sho will precipitate death by reducing the critically lowered cardiac ou put to a level incompatible with survival

Since this chapter was first written, new evidence (to be published) has bee accumulated which indicates that the "congested" liver may result, not from capillary atony (Prinzmetal) or from arteriolar atony but from venous spasm within the liver This might also be the case for other viscera. Capillary stagnation in such viscera might then be explained not only on the basis of deficient arteriolar tone and low arteriolar pressure but also on the basis of increased venous resistance.

It is perhaps of no great consequence whether the blood content of tissues at any moment is the same somewhat more or somewhat less than normal. But the proportion of this blood in active circulation through tissues is of paramount importance The capillary bed normally contains some 20 per cent of the total blood volume In untreated shock this percentage is not only not increased but probably is decreased. Direct estimations of the blood content of the

applied for some hours to an extremity is an unusual clinical condition it is of more than academic interest, being comparable to clinical shock resulting from conditions such as burns intestinal obstruction, or certain high velocity projectile wounds in which a large and more or less rapid loss of plasma from the circulation is the shock inducing agent The special features of these various conditions obscure the effects of the mere loss of plasma. Tourniquet shock constitutes a more controllable and possibly less complicated type than others for an experimental study of shock resulting primarily from plasma loss.

One would anticipate that shock involving pure plasma loss should be as responsive to plasma replacement therapy as is hemorrhagic shock to whole blood replacement therapy In numerous early studies of tourniquet shock there was almost uniform agreement that death usually occurred regardless of the therapy employed unless the tourniqueted extremities were refrigerated immediately upon release of the tourniquets or tightly taped so as to prevent the escape of plasma from the circulation (2 4,8,9 13,20,45,68,81,85) That taping is sufficient to prevent the onset of shock would argue against any relationship between the onset of shock and the damage inflicted upon the muscles at the site of application of the tourniquet. It is therefore not surprising to note the failure to date of efforts to isolate an etiologically significant "toxin" from the crushed muscle (see the discussion below on toxic factors)

In these circumstances it is all the more perplexing that early and adequate replacement of the plasma lost into the injured extremities should have failed to cure the shock state. An evaluation of the experimental set up and of the effectiveness of replacement therapy was therefore regarded as necessary

It was later shown (24) that if the proper circumstances are created adequate replacement therapy can be curative Nearly all earlier experiments had been carried out under barbiturate anesthesia. The unfavorable effect of anesthetics on the shock state led to the avoidance of all anesthetics or sedatives except morphine sulfate (3–6 mg./Kg.) given intravenously or intramuscularly before and once or twice during the application of the tourniquets The extremities became insensitive after some time and no further drug was necessary (a few exceptional instances required a single supplementary dose of 10 mg. intramuscularly) so that the experiment

thereafter was carried through without further medication except therapeutic substances as noted below

Tourniquets were applied to both legs for 5 hours, the interval usually employed by previous investigators Upon release of the tourniquets, the extremities swelled, but shock was either slow to appear, frequently not until 5 to 7 hours later, or it did not occur at all. Furthermore, the shock state so induced was effectively treated by physiologic saline solution alone. This was contrary to all previous experience, and the difference was regarded as due wholly to the omission of barbiturates

To induce rapid and severe shock, the technic was altered by merely prolonging the time of tourniquet application to 8 to 11 hours. Nearly all such dogs (79 out of 80) developed profound shock. If no treatment was given, death usually resulted in less than 6 hours and always in less than 12 hours Autopsy showed extensive muscle damage with degeneration of muscle fibers and some hemorrhagic extravasation into the crushed muscle. The swelling distal to the site of tourniquet application was pronounced, but it did not occur until after removal of the tourniquets. The arteries and veins were patent, and there was no evidence of mechanical interference with blood flow during the shock state.

Following release of the tourniquets, the lower extremities were not incised or otherwise manipulated for such extremities are readily infected. Accordingly in most of the experiments blood sampling and intravenous therapy were done under local anesthesia in the neck. The data gathered included determinations of arterial and venous oxygen concentration oxygen consumption cardiac output, arterial hematocrit and arterial blood pressure before shock, and before and after therapy during shock.

The experiments were usually carried out by studying a given type of therapy in 5 or 6 dogs simultaneously thus eliminating variations in response to tourniquet application which seem to depend on environmental conditions. (For example, dogs go into very rapid and severe shock more readily on hot, humid days.)

After release of the tourniquets, the dogs became quiet and apathetic the legs swelled rapidly and shock was obviously present before the blood pressure began to fall, as indicated by the dull apathetic state of the animal and an already markedly lowered cardiac output. In 61 dogs therapy was started only when the blood

pressure had fallen to 70 mm. Hg or lower While this level of blood pressure is regarded as "the critical level" in hemorrhagic shock, a higher level is critical for tourniquet shock (page 40) Hence the treatment may be regarded as having been applied after poor blood flow had been present for some time.

The therapy given was intended only for cure of the shock state Successful therapy signified recovery from shock and survival for a minimum of 24 hours after removal of the tourniquets regardless of whether or not the dog subsequently died or was sacrificed because of massive necrosis or sepsis. It is possible that an occasional dog who died before the 24 hour period succumbed in part to sepsis since streptococci and Clostridium welchii were found in the leg muscles of many and in the heart s blood of some of these dogs. Such dogs were regarded as dead from shock.

The therapy given was of four types (*1*) Crystallized bovine serum albumin, given intravenously in 25 per cent solution containing 1.5 per cent NaCl or in 5 per cent solution containing 0.9 per cent NaCl. (*2*) In certain experiments with 25 per cent bovine albumin, water or 0 9 per cent NaCl was given by stomach tube and repeated to the limit of gastric tolerance. (*3*) 0 9 per cent saline solution intravenously (*4*) 5 per cent saline solution, intravenously together with water by stomach tube.

The detailed results are available elsewhere (34) The following conclusions were derived from them (*1*) Isotonic and hypertonic saline solution in moderate to large volumes is of no therapeutic value except perhaps in very mild tourniquet shock. (*2*) Plasma and 5 per cent bovine albumin in 0 9 per cent saline solution is therapeutically effective. (*3*) 25 per cent bovine albumin equivalent to 5 per cent bovine albumin in protein but not in salt and water content, was effective only if isotonic saline solution by mouth was added. (*4*) When therapy was successful the characteristically high hematocrit values fell to normal or subnormal values with a simultaneous increase in circulating plasma volume when therapy failed the hematocrit, as a rule remained elevated and circulating plasma volume did not increase

In the case of intravenous saline solution alone the insufficiently reduced hematocrit was due to a failure of intravascular retention of the infused fluid In the case of 25 per cent albumin solution alone it was due to the limited volume of fluid available in the

interstitial fluid reservoir, as was evident from the extraordinarily dry state of the tissues produced by the strong osmotic effect of the albumin When, however, intravenous administration of 25 per cent albumin was supplemented by saline solution via stomach tube, the saline was effectively absorbed and retained by the circulation, as indicated by the extent of the rise in plasma volume, and recovery occurred A fall in the hematocrit level to normal or less than normal accompanied the increase in plasma volume in the 10 instances in which such data were obtained 8 of these 10 dogs survived

From the foregoing data, it appears that blood substitutes in the form of plasma, 5 per cent bovine albumin in 0 9 per cent sodium chloride solution, or 25 per cent bovine albumin plus supplementary fluids by stomach tube are effective therapy in tourniquet shock. There were 30 dogs receiving such therapy, 22, or 73 per cent, recovered in 6 of the 8 who died, therapy was applied at a systolic blood pressure below 60 Only 5 of the 22 surviving dogs received therapy after the blood pressure had dropped below 60 Dogs in tourniquet shock are in an advanced state of collapse when the blood pressure is 70 a mean pressure of 60 may therefore be regarded as close to the permanently irreversible level in tourniquet shock.

Since replacement of deficient blood volume is curative tourniquet shock results from oligemia and not from a toxin To what extent toxins liberated from damaged muscle or ischemic tissue play an adjuvant role cannot be assessed Their minor consequence is clear from the fact that the effective therapeutic agents do not neutralize toxins and because taping, which prevents shock, can do so only by preventing loss of blood volume and not by interfering with absorption of toxins. Necrosis and infection which occur following recovery from tourniquet shock are sequential or adjuvant phenomena bearing no direct relationship to the rapid collapse *immediately pursuant* to the release of the tourniquets. There is accordingly no difference between hemorrhagic and tourniquet shock in respect to the type of agent responsible for initiating the shock state.

Significant differences between the phenomena of hemorrhagic and tourniquet shock do exist however, and these modify the course of events, as well as the kind of therapy applicable in each. These differences are tabulated in Table VIII The most remarkable physiologic differences are in the level of blood pressure at which

shock may be said to exist (the critical blood pressure), the tolerance to bleeding at low pressures, and the hematocrit level.

As already indicated the blood pressure level is grossly misleading in tourniquet shock. The legs rapidly swell immediately upon release of the tourniquets, and though a large loss of plasma has occurred the blood pressure tends to remain at some 100 mm. Hg for an hour or two thereafter Even so, the dog is obviously sick.

TABLE VIII
Differences in Phenomena of Hemorrhagic Shock and of Tourniquet Shock (24)

	Hemorrhagic shock	Tourniquet shock
Fluid loss into localized areas	None	Large
Blood deficiency	Whole blood	Plasma slight volume of red cells
Hematocrit level	Normal or low	65 to 85 per cent
Critical level of mean blood pressure	80 to 70 or less comparatively well tolerated for hours	100 or less levels below 70 poorly tolerated, followed shortly by rapid and irreversible collapse
Relationship of blood pressure level and its duration to curability	±30 tolerated for hours	Below 40 tolerated for minutes
Capillary circulation	Slow flow capillaries contain few red cells	Slow flow but capillaries contain many red cells
State of sensorium	Dull at blood pressures much below 70	Dull at pressures below 100
Tolerance to blood sampling	Good until very low pressures are reached	Poor at pressures between 80 and 100

The cardiac output may be as low as 25 per cent of normal and the venous oxygen concentration 5 per cent by volume within 15 minutes after release of the tourniquets. Once the blood pressure begins to fall, it falls precipitously Withholding therapy until pressures are reached which are considered reasonably safe in hemorrhagic shock is likely to be disastrous. Therapy at pressures of 100 to 70, however may be expected to be effective.

With the evidence that the safe interval for transfusion is much shorter in tourniquet shock than in hemorrhagic shock, that the appropriate fluid must be supplied before the blood pressure has fallen very far and that volume replacement therapy is effective in both, it became obvious that the critical difference between the two conditions would seem to be confined to differences in the nature

of the hemodynamic imbalance. Among these differences, the high hematocrit level is the most distinctive feature so that its signifi cance in relation to the onset of irreversibility requires detailed evaluation.

Blood Viscosity in Relation to Irreversibility

It has long been realized that the increased viscosity due to a high hematocrit may impose an additional load upon an already embarrassed circulation, and so may aggravate the shock state Accordingly an extensive study of the effect of high hematocrit levels upon blood pressure, peripheral resistance, and cardiac output in both tourniquet and hemorrhagic shock was made (75) Poiseuille's equation

$$\text{flow} = \frac{\text{pressure}}{\text{resistance}} \times \text{constant}$$

was adapted to a system composed of nonrigid tubes and containing a nonhomogeneous fluid as follows

$$\text{cardiac output} = \frac{\text{blood pressure}}{\text{total peripheral resistance}} \times K$$

The total peripheral resistance is the product of the blood viscosity (n) and the resistance (R) determined by the number length, and caliber of peripheral vessels. Cardiac output, blood pressure, and blood viscosity are determined directly The details of the method used for measuring n and for deriving R have been published elsewhere (75) Once these values and their interdependence are known, so that a constant (K) for the normal animal can be evalu ated, a standard is provided for the purpose of making comparable observations upon the dog in shock.

It was found that (*1*) an increase in blood viscosity has a deleterious effect upon cardiac output when the blood volume is deficient (*2*) restoration of a high hematocrit value to normal or below normal improves cardiac output, but the increase in cardiac output is not enough noticeably to improve the shock state unless volume deficiency is restored simultaneously, (*3*) at any level of reduced cardiac output, the arterial blood pressure is higher when the blood viscosity is elevated, so that a deceptively favorable impression of the state of the circulation is given by the blood pressure reading. Hence at blood pressure levels which are con

sistent with only a mild degree of hemorrhagic shock, the cardiac output in tourniquet shock is already disproportionately low

Accordingly, it is clear that the increased hematocrit value of tourniquet shock is a liability over and above that of volume deficiency and can account for the observed differences between tourniquet shock and hemorrhagic shock. Volume deficiency is by far the greater danger and the restoration of blood volume is a more urgent need than is that of normal viscosity If an abnormally high viscosity exists in shock and is not treated effectively the restoration and maintenance of normal blood volume becomes even more imperative. These findings explain the development of irreversibility to transfusion and the poor tolerance to bleeding at higher levels of blood pressure in tourniquet than in hemorrhagic shock.

These studies do not suggest that there is a distinction in the fundamental nature of the disturbance between these two types of shock. The postulate of Chambers *et al*, namely that a humoral vasoexcitor substance appears in the early phase of shock as a compensatory mechanism in response to the falling blood volume and that subsequently a vasodepressor substance appears as compensation fails and irreversibility sets in applies to both types of shock. In spite of slight differences in capillary flow during the hyporeactive phase in these types of shock the basic manifestations in the peripheral circulation are identical.

Therapy of Irreversible Hemorrhagic Shock

Until recently most therapeutic efforts were concerned with attempts by many investigators to restore hemodynamic equilibrium by one or another variety of fluid replacement therapy Others have tried and claimed success with pressor agents, by correcting acidosis or more recently, by therapy calculated to correct fundamental disturbances in cellular respiration. Still others, concerned with the disturbed function of individual organs, have dealt with the possibilities of therapy designed to restore their function. If we are to expect some orderly progress in the search for an understanding of the basic pathologic physiology the information which such therapeutic methods provide should be assessed in terms of rigid standards for testing therapeutic agents. The standard we have adopted is the creation of a state of shock irreversible to transfusion, produced as described above.

The following agents were studied with the foregoing considerations in mind. (*1*) Saline solution in large volume, (*2*) whole blood, (*3*) 5 per cent and 25 per cent albumin solutions, (*4*) pressor agents, (*5*) alkali, (*6*) succinic acid, thiamine, coramine, cytochrome c, and other special substances, (*7*) various combinations of the foregoing agents, (*8*) cross circulation of the liver by a healthy dog.

Utilizing hemorrhagic shock induced according to the technic described above, and eliminating as far as possible anesthetics, operative manipulations, and other forms of trauma which facilitate the development of irreversibility or otherwise complicate the shock state, the agents listed were studied in most instances only after the shock state was found to be unresponsive to the replacement of all shed blood. The results obtained have been discussed in detail elsewhere (32) The following summarizes the findings

(*1*) Massive infusions of physiologic saline solution may cause transitory improvement in circulation, but do not cure hemorrhagic or tourniquet shock irreversible to transfusion

(*2*) Once the initial transfusion has failed no amount of whole blood or plasma achieves more than a transitory pressor response.

(*3*) Massive infusions of isotonic (5 per cent) bovine albumin solution greatly increase the blood volume and may sustain the circulation for a time, but only rarely result in recovery A marked bleeding tendency is produced by this therapy Concentrated (25 per cent) bovine albumin solution with equivalent or greater protein content is of no benefit, even if supplemented by saline solution.

(*4*) Large volume intravenous infusion therapy, using either physiologic saline alone or albumin in physiologic saline solution is harmful because it produces marked edema of tissues, pulmonary edema, serous effusions, venous distention, and widespread hemorrhage from small vessels.

(*5*) Most vasopressor drugs are considered deleterious they add to the already increased vasoconstriction, with the result that capillary flow is further depleted. This is particularly true when epinephrine or neosynephrine is given, epinephrine having the further unfavorable effect of increasing tissue metabolism. Pitressin, with or without ergotamine, is of no value, and pitressin combined with 5 per cent albumin solution is not beneficial. Observation of the capillary flow in the exteriorized omentum graphically and indisputably shows the extremely damaging effect these drugs inflict on the blood flow through tissues Paredrine raises the arterial and

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ing hemoconcentration due according to Fox (30) to swelling of red cells Accordingly these authors recommend large volumes of saline solution (122 cc./Kg.) to restore fluid and electrolyte balance and plasma volume (40)

This amount of salt is obviously far beyond the deficiency existing, for example in experimental shock from hemorrhage Thus a 40 per cent blood loss in a 10 Kg. dog constitutes a salt loss of some 2.5 Gm. If the basic deficiency is salt loss, the 12.5 Gm. recommended is excessive. In the clinical treatment of shock, the volume of saline solution recommended, if given parenterally is likely to produce pulmonary edema. There are no data on the degree of shock in burned patients treated by these authors with fluid and electrolyte. If they were drinking and absorbing large quantities of sodium solutions, it is not likely that they were in severe shock since intestinal absorption in shock is deficient. If they were voiding urine freely they were presumably not in shock, or only in mild shock.

These effects of trauma upon fluid and electrolyte balance are *equivalent to those resulting from acute salt loss produced experimentally* by Winkler *et al.* (92) and others (17,22), who state that the shock produced by acute salt loss is responsive to full replacement of the lost sodium by saline solution or by gelatin or plasma containing from 20 to 30 per cent of the salt loss The same amount of salt without protein is not effective, nor is salt free gelatin or plasma. There is of course no doubt of the value of salt solution where a salt and water deficiency exists, as is often the case in shock, particularly in burn shock or in any state of acute dehydration. It is hardly credible however that salt and water deficiency except in the case of acute salt loss, is the basic phenomenon in the shock resulting from hemorrhage or muscle trauma. In these conditions it has been found that (*1*) There is no change in interstitial water and electrolyte balance in the uninjured tissues or in plasma sodium or chloride in dogs (40) (*2*) Saline solution in ample volume *is of little or no value* in 8 to 10 hour tourniquet shock, while plasma or 5 per cent albumin is curative. (*3*) The response in advanced hemorrhagic shock to saline solution is feeble in comparison with the response to blood or a blood substitute. If the shock induced by simple hemorrhage results from sodium depletion one should be able to reverse the shock process by infusion of the salt and water content of the blood lost. This is clearly not the case (*4*) As will be shown below perfusion of the dog in shock via the splenic vein by a donor dog cures shock which has failed to respond

to transfusion, while perfusion of the dog in shock via the jugular vein does not.

We have repeatedly noted the fact that dogs in hemorrhagic or tourniquet shock treated unsuccessfully with intravenous solutions show wet tissues including pulmonary edema, hemorrhagic intestinal mucosa, or both, whereas dogs dying of shock who have received no intravenous fluids do not show wet tissues or hemorrhagic intestinal mucosa (except in burn shock) It is our inference that wet tissues are due (*1*) to failing capillary circulation which, because of sluggish and reduced volume flow of blood that is frequently hypoproteinemic, cannot absorb via the venous end of the capillary a solution which readily escapes from the arterial end (*2*) to reduced lymphatic return of tissue fluids to the circulation (except perhaps in burns) Wet tissues may therefore occur because the balance between the normal rate of escape and return of water and electrolytes may be upset for reasons unrelated to a structural alteration affecting the permeability of capillaries. Such wet tissues are much less readily produced by infusions of concentrated albumin whole blood or plasma. The evidence is that wet tissues are not a phenomenon of shock but merely the result of using excessive amounts of simple electrolyte solutions when shock is present. It is therefore urgent that in a patient in shock the actual deficiency in water and salt be carefully estimated. The uncontrolled administration of water and electrolytes is especially dangerous when renal function is impaired.

The acidosis of shock is in part due to dehydration and in part to metabolic disturbances resulting from anoxia. For this reason alkali therapy was originally recommended by Cannon and more recently by others (49) The acidosis of shock is progressive, and no doubt deserves correction along with any existing water and sodium deficiency Ingraham and Wiggers (44) report that the onset of irreversibility in hemorrhagic shock is delayed by the use of sodium bicarbonate throughout the hypotensive period. On the whole, the disappointing results from alkali therapy in shock do not argue against its validity but they do give point to the probability that acidosis is an accompanying phenomenon and plays only a secondary role.

In appraising the value of any agent other than blood or a blood substitute the conditions prevailing at the time of testing must be

as free as possible of complicating factors Thus, the beneficial effects of pitressin with or without ergotamine observed by Cham bers *et al.* (12a–b) cannot be safely inferred from their results, because the drug was given with or just *after a transfusion.* We observed no benefit from pitressin or any other pressor drug if given before transfusion, or after transfusion had failed to have failed.

On the same basis, we were unable to confirm the findings of Kohl staedt and Page (46), who identified by cardiometric observations on the exposed heart in shock, a measure of cardiac weakness which was not reversible by any known methods of therapy and found *that certain aliphatic amines* ("one-amine,' "tuamine,' etc.) with specific myocardial stimulating qualities were able to cure the shock state. In 6 experiments with our technic of determining irreversibil ity tuamine produced no rise in cardiac output or other beneficial response except a transient rise in systolic pressure. The effect of tuamine was analogous to that of paredrine. Our experiments differed from those of Kohlstaedt and Page in that they gave the drug with or immediately after transfusion whereas we withheld the drug until the response to transfusion alone had been found in effective.

The tolerance of the organism to hemorrhage, when the latter is induced by the withdrawal of blood by simple needle puncture of a large artery in the intact unanesthetized and unimmobilized dog, contrasts sharply with that of the dog anesthetized immobilized cannulated and otherwise traumatized. This points to the need of excluding, as far as possible all extraneous factors if the shock due to volume loss alone is to be properly evaluated Experiments re ported by Schachter (72) are a case in point. He reports that chol inesterase cures traumatic shock induced by intestinal manipulation in anesthetized hyperthyroid dogs. From his hematocrit data, there is reason to believe that the plasma volume loss would not have been sufficient to induce fatal shock in unanesthetized nonhyperthyroid dogs. Presumably, shock was precipitated by the superimposed ag gravating factors of barbiturate anesthesia and hyperthyroidism Plasma volume therapy failed in such dogs for the same reason that it fails in 5 hour tourniquet shock induced under barbiturate anes thesia. The favorable action of cholinesterase in these experiments may have been exerted upon the accessory aggravating factors and

does not justify a conclusion that cholinesterase is of value in the treatment of shock per se.

The more extraneous factors are eliminated from the experimental set up the more difficult it becomes to produce irreversibility to transfusion, which then is achieved by prolonging the time and increasing the degree of hypotension. Our experiments approached the ideal of simplification only very approximately, for we used morphine and a considerable degree of immobilization in order to obtain essential data not otherwise possible. Furthermore, we did not prevent bacterial contamination. The factor of sepsis, however is of dubious import because of the absence of pathologic evidence of its presence in these experiments and because the experimental period seems too short for the production of significant amounts of bacterial toxin. Even if bacteremia is common in these circumstances it remains to be shown that the kind of organisms, their number and their virulence, were of sufficient importance during the period of experimentation to have influenced the results

Reduced to the simplest conditions it is practical to achieve experimentally, we believe that the course of events in hemorrhagic shock leading to the development of a state of irreversibility to transfusion is a function of the severity and duration of inadequate capillary flow with a resulting, cumulatively adverse effect on the integrity of cellular function.

Evidence of recovery from shock includes a sustained rise in cardiac output, in acceleration of capillary flow in oxygen content of the mixed venous blood, and in blood pressure. Such changes, readily achieved during the early shock phase by transfusion, do not persist following the infusion of large volumes of fluid of any kind given after the initial transfusion has failed. The futility of infusion in advanced shock of large volumes of fluids, including those which do not escape or escape only slowly from the circulation demonstrates that conditions exist which require something more than the restoration and maintenance of a normal blood volume.

While the critical deficiency in late shock may lie in an altered physiology of the circulation independent of controlling factors outside the circulation it is natural that such controlling factors should also come under scrutiny since the effect of inadequate flow is all embracing.

FUNCTIONAL CHANGES IN INDIVIDUAL ORGANS OR TISSUES

Muscle Tone Henderson (43) attributes the circulatory fault in shock to a loss of skeletal muscle tone with consequent failure of venous pressure and return flow In our experiments with coramine, which increases skeletal muscle tone to the point of extreme rigidity, blood flow was not improved. A more desirable physiologic technic to test the Henderson hypothesis would provide for alternating con traction and relaxation of muscle.

Nervous System The studies of Cannon and others relative to the nervous system served to exclude a disturbance in its functional integrity as a factor in the development of irreversibility The vasomotor system was shown to be intact until the prelethal phase of the process, and the loss of vasomotion in advanced shock, so well demonstrated by Chambers *et al.*, is explained on a humoral basis.

Swingle *et al.* (80) revived the theory that nociceptive stimuli from the area of injury induces or intensifies shock, on the ground that spinal anesthesia markedly reduced the incidence of shock resulting from muscle trauma to an extremity Local procaine block provided protection to a lesser degree. However, section of the spinal cord or the main nerve trunks did not prevent shock. The extent of local fluid loss was not measured and the hypotensive effect of spinal anesthesia was not considered. Phemister and Schachter (61) and Phemister (60) demonstrated that the protective effect of spinal anesthesia was due to decreased bleeding into the injured area con sequent to the reduction in blood pressure for the same protection could be provided by preliminary ligation of the large artery supplying the injured area in the absence of spinal anesthesia. Prior section of all dorsal spinal nerve roots below the twelfth thoracic provided no protection

Phemister produced neurogenic shock by prolonged stimulation of the cardioaortic nerves. This caused marked hypotension reduced blood oxygen and carbon dioxide concentration, and exhaustion of the vasomotor center after 4 to 7 hours But removal of the stimulus at any time before collapse of the vasomotor center was followed by rapid recovery These effects were not elicited by prolonged stimula tion of somatic nerves Nothing paralleling such experimental condi tions occurs in man. The neurogenic factor is of little or no impor tance except that if hemorrhage sufficient to lower the pressure to

shock levels is followed by central vasodepression induced by direct nerve stimulation such as by abdominal manipulation, shock may be intensified. But prolonged hypotension alone in the absence of blood loss is tolerated very well The role of the nervous system has thus been extensively studied, with little evidence to incriminate it.

Kidney Oligemia or anuria is one of the first signs of shock. The limit of the kidney's tolerance to anoxia, and its capacity to resume function following graded degrees of exposure to anoxia, has been defined (63) When the blood pressure falls to 70 mm. Hg in hemorrhagic shock, a sharp reduction in renal blood flow occurs and with it a disproportionate fall in oxygen consumption due to the kidney's inability to extract more oxygen from the blood, in contrast to the rest of the organism which is able to do so. In crush injury the disturbance in renal function appears even earlier so that urine flow, excretion of creatinine, and extraction of *p*-aminohippuric acid stop when the blood pressure falls below 100 mm. Hg. This renal injury is similar to that produced by incompatible blood, but cannot be induced by sterile purified hemoglobin unless renal ischemia is superimposed. Ischemia of 4 hours duration results in eventual death from renal failure Van Slyke (84) found hepatic damage along with the renal injury but it is not clear that the disturbances are interrelated. Since the effect of renal damage on the organism is not operative within the shock period it is not likely that renal ischemia contributes to the intensity of the shock or to the onset of irreversibility Nor is it likely that there are depressor substances which are excreted by the normal kidney but which, when retained because of renal failure, cause irreversible shock, since shock does not result from bilateral nephrectomy except as a complication of uremia.

The ischemic kidney excretes increased quantities of renin. This may be regarded as a protective mechanism against existing or impending hypotension, except that the rapid exhaustion of hypertensinogen (18) in shock makes its presence of doubtful value Its importance as a defense mechanism in prolonged hypotension is dubious since its excretion must fall toward zero as ischemia increases, and because the complete absence of renin in bilaterally nephrectomized dogs subjected to hemorrhagic shock does not appear to affect their tolerance to bleeding.

Van Slyke (84) emphasizes that the dog's kidney shows greater tolerance to anoxia than the human kidney Thus the lower capacity

of the human kidney to recover from the effects of shock is not infrequently followed by uremic manifestations in the recovery period which are rarely observed in the dog. It is far from certain, however that the uremia seen after recovery from extensive muscle trauma in wounded men, which is frequently fatal, is due to the effect of shock alone.

The uremic failure following severe trauma is probably reversible, and therefore led to a study of peritoneal irrigation as a technic for its treatment.

Intestines In hemorrhagic shock, the small intestine shows a marked and progressively deficient capacity for the absorption of glucose and water (38) This is perhaps to be expected, since the absorption of water presumably requires the delivery of electrolytes from the blood into the bowel and glucose requires phosphorylation, which is deficient in shock. At the same time, because of poor blood flow, it is rather surprising that the absorption of isotonic saline solution is not deficient until very advanced shock is present. These phenomena were observed in hemorrhagic shock and in 6 experiments in tourniquet shock (24b) In the latter series, therapy consisted of intravenous administration of 25 per cent albumin supplemented by isotonic saline solution fed by tube 5 of the 6 dogs survived. In 6 other experiments on tourniquet shock, in which intravenous administration of 25 per cent albumin was supplemented by water fed by tube, absorption of water was sufficient in only 3 instances to provide the necessary fluid to restore effective circulating volume.

Heart Cardiac reserve is well sustained, as indicated by improvement in cardiac output in response to transfusions even in late shock. This latter observation has been made repeatedly in all types and degrees of shock until the prelethal phase It is therefore generally agreed that failure of cardiac function is not of primary importance in shock, in spite of the progressive decline in cardiac output. The evidence adduced by Kohlstaedt and Page (40) and especially by Werle, Wiggers, and others (37,38) that a measure of myocardial weakness exists in shock may be regarded as an index of damage from prolonged anoxia a condition which must affect the function of all tissues adversely No bacterial toxin capable of producing shock has been shown to do so as a result of a direct effect on the heart, with the possible exception of the diphtheria toxin. In a

heart–lung preparation, the declining cardiac output following the administration of Clostridium welchii toxin was found to be due to damage to pulmonary capillaries, and not to cardiac damage (3a) These observations do not, of course, exclude the possibility that shock may develop as a result of cardiac damage Shock following coronary thrombosis, myocardial infarction or cardiac tamponade is a well recognized clinical syndrome.

TOXIC FACTORS

That severe infection can precipitate shock is a common clinical observation. The induction of all the features of traumatic shock by bacterial toxins has been amply demonstrated in the experimental animal (36) The predisposition to shock in patients with infection subjected to surgery is well known. Recently, Mahoney *et al.* (51) have shown that dogs suffering from a localized infection go into shock in response to a lesser degree of trauma or blood loss than normal dogs Presumably infection, like malnutrition, cachexia, and other conditions deprives the organism of some as yet unknown principle whose function it is to resist the onset of peripheral circu latory collapse.

The concept of resistance to shock and the development of immunity to the shock-producing effects of trauma has been demonstrated in rats which survive prior exposure to a sublethal number of falls in the Noble-Collip drum (56,83) This immunity can be enhanced by prior forced feeding with a high protein diet (78) It appears that sublethal trauma sets up a reserve supply or permits a rapid mobilization of metabolic reserves which counteract the energy-depleting effects of trauma.

The bacterial toxins of Cl. welchii and related organisms were found in the fluid collected from a muscle in the dog following the release of its occluded blood supply (55) Such toxins by splitting lecithin in red cells and elsewhere can induce typical traumatic shock. If given intravenously, no substantial fall in plasma volume results, if given intramuscularly plasma loss and hemoconcentra tion occur The shock inducing effect of such toxins is not so severe if blood loss or anesthesia is avoided, thus serving to emphasize the additive effect of one etiologic agent upon another

The presence of the gas bacillus in the muscles injured by the application of tourniquets does not establish a case for the etiologic

significance of this organism in tourniquet shock. The reasons are (1) Shock due to Clostridia toxins cannot be cured by plasma or albumin therapy Tourniquet shock can be cured by these agents. (2) Death from tourniquet shock is extraordinarily rapid, a matter usually of a few hours following release of the tourniquet, so that too little time is available for a lethal amount of bacterial toxin to develop (3) The amount of fluid transudate from muscle infected by Clostridia required to induce fatal shock was usually far in excess of that produced by a single animal. (4) The type of shock produced by Clostridia toxins, particularly the severe hemolytic effect of such toxins, is not seen in tourniquet shock. (5) There is no correlation between the number of organisms cultured from damaged muscle and the severity of shock, some of these organisms, in fact, did not produce potent toxin. (6) Change in the course of tourniquet shock by pretreatment with antitoxin has not been demonstrated

However, the shock which appears after many hours following the release of a crushing clamp to the hind limb of the dog is probably due to a toxin The fluid loss immediately after removal of the crushing clamp is often insufficient to induce shock, whereas the shock which appears some 12 to 24 hours later can be prevented by chemotherapy

Many investigators believe that nonbacterial toxins of endogenous origin are capable of producing traumatic shock. Kallikrein, of tissue origin, can produce shock (89), but there is no evidence that it is set free in the circulation during shock. An endotoxin from damaged muscle has been postulated (11) Page (58) believes that the renal damage from muscle crush injury is due to hemoglobin derivatives or to myoglobin from damaged muscle. But no convincing evidence has been brought forth to show that renal injury or the factor responsible for renal injury is responsible for the shock which may develop from the muscle trauma. Prinzmetal (8,65,66) regards the phenomenon of trapping in the peripheral circulation as due to a toxin, because congestion of the kidney and heart muscle and decreased bleeding volume occur in the rat within one minute after producing a hot water burn. Chambers and his collaborators believe that the hyporeactive state of the arterioles and precapillaries in late shock is due to a circulating vasodepressor agent, since the blood of shocked dogs reproduces the same state transitorily in the mesenteric circulation of the rat.

Shorr *et al.* (78) have demonstrated a vasodepressor principle in ice-cold saline washings of liver from shocked animals This principle is not demonstrable in other tissues except in lesser concentration in muscle and in still smaller concentration in blood. They isolated the vasodepressor substance not only from the liver tissue from shocked animals but also from normal liver kept in an oxygen free environment for more than 2 hours This substance, moreover was inactivated by normal liver tissue and by anoxic liver after re-exposure to oxygen for 2 hours This led them to regard the peripheral vascular collapse as due to the action of a vasodepressor substance derived from anoxic liver

Such a postulate is more logical than the theory of a nonbacterial toxin derived from damaged tissue since the peripheral collapse is present in a variety of shock states in which no overt damage exists except as the prolonged anoxic state eventually damages all tissues. Nevertheless it has been argued that the more precarious state of a dog in tourniquet shock (in which muscle is severely damaged) as compared to the dog in hemorrhagic shock, is due to the absorption of toxins from the site of injury This conclusion seemed to follow from the observation that adequate volume replacement therapy was ineffective in dogs in shock following release of tourniquets applied for 5 hours Swingle (81) showed that the application of plaster casts, immediately after release of the tourniquet, so as to prevent swelling, prevented shock. Since the circulation was not interfered with, toxins, if present should have been absorbed. It was later shown (24) that if barbiturates are omitted shock is mild or absent when tourniquets are released after application for 5 hours, and that the failure of volume replacement therapy was due to the intensification of the shock state by the barbiturates used as the anesthetic agent. When tourniquets were applied from 8 to 11 hours without barbiturates (morphine only being used during the early phase of tourniquet application) deep shock resulted. But even this degree of shock responded favorably to volume replacement therapy Since the therapeutic agents used i.e., plasma 5 per cent bovine albumin, etc., are incapable of neutralizing toxic agents the theory of shock due to a locally elaborated toxin received no support. It was demonstrated therefore that plasma loss constituted the major if not the sole, etiologic factor in tourniquet shock.

METABOLISM

Shock is a state of rapid biologic disintegration. Extreme alterations in labile equilibria especially those affected by anoxia, are *therefore to be expected. All oxidation* reactions so far investigated have been found to be abnormal. The phosphorylation of enzymes (39 41) the conversion of lactic and pyruvic acids to carbon dioxide and water and the resynthesis of adenosine diphosphate and triphosphate from adenylic acid are disturbed (48,50) It follows, *therefore that cellular respiration must be profoundly affected.* This has led to an inquiry into the possible value of the substrate, cytochrome c as a means of restoring normal oxidative function. This tissue protein activates the cytochrome–oxidase enzyme, and permits a greater extraction of available oxygen. Proger *et al.* (67) observed improved function in states of relative anoxia after intravenous administration of cytochrome c. In collaboration with these investigators, Seligman Frank, and Fine (73a) tested this enzyme in hemorrhagic shock. When it was given early in the reversible phase no clear benefit was conferred When it was injected *after* irreversible shock was present *and full-blown, no clear benefit* could be seen, although the speed of taking up was considerably slowed However of 15 dogs to whom this enzyme was given as soon as taking up started and before transfusion was given 9 (60 per cent) survived which is in excess of the expected survival rate for dogs in *this degree of shock. While this therapeutic result is more* promising than was to be expected from any substance other than blood, hitherto investigated, failure to prevent the onset of irreversibility to transfusion or to correct the latter, once established, suggests that cytochrome c at best, possesses only adjuvant therapeutic property *A striking phenomenon following its use in early hemorrhagic* shock is an increase in bleeding volume, demonstrated by an immediate outpouring of blood from an artery connected to an elevated reservoir containing the shed blood without a change in the prevailing blood pressure. Since no further drop in blood pressure occurs, it may be that cytochrome c improves vascular tone, presumably by correcting anoxia of the peripheral blood or in some tissue controlling the vessels.

Temperature Effects

The anoxemia in shock is severe and progressive, so much so that the oxygen concentration in the blood of the right auricle may be close to zero Tissue anoxia cannot be improved by oxygen therapy for even when the oxygen saturation of venous blood was increased to normal levels by breathing 100 per cent oxygen at a pressure of 2 to 3 atmospheres there was no noticeable improvement in the shock state (83) (Had it been possible for us to carry out this experiment without anesthesia, benefit from oxygen so used might have resulted) Tissue anoxia is not relieved in these circumstances probably because the capillaries are out of contact with the active circulation. Progressive biochemical disintegration is therefore inevitable. An increase in local or environmental temperature in this situation is likely to be harmful and recent studies have demonstrated this to be the case beyond any doubt (86a) In experimental muscle crush injury in the dog gas formation, fever, and early death occurred when the environmental temperature ranged from 24 to 27 C., whereas at temperatures between 16 and 20 C gas formation was inhibited Death from muscle injury to one leg was reduced from 100 per cent at 28 C to zero at 16 C Refrigeration of a crushed leg, even at a room temperature of 28 C., resulted in survival. Refrigeration of a tourniqueted extremity before release of the tourniquet prevented death from shock. The use of ice packs applied soon after release of the tourniquet prolonged survival time (20) In animals dying from this injury the blood changes were all in the direction of hemoconcentration, i.e plasma loss Shock induced by the release of tourniquets appears early and is cured by volume replacement therapy but not by chemotherapy shock from muscle crush injury appears late i.e. after some 24 hours is prevented by chemotherapy and is presumably due chiefly to bacterial action (8) Hence the protective effect of lowered local or environmental temperature is due to the vasoconstrictive action of cold which reduces the loss of fluid into the injured extremity or to inhibition of the invariably superimposed infection, or to both. It is a commonplace experience among investigators of shock that a hot humid environment is most unfavorable for shocked animals This is to be expected the deleterious effects of high temperature upon metabolic exchange in anoxic states being well known. It follows that in the

treatment of shock body heat should be conserved, but addition of any external source of heat be avoided and where possible environmental temperature reduced to some 16 to 24 C

Anesthetics and Analgesics

The integrity of tissue function is also likely to be adversely affected by anesthetics. The intensification of the depth of shock by anesthetics has long been recognized Surgeons discovered the dangers of ether nitrous oxide, and spinal anesthesia in shock, even though the mechanism of their disturbing action was not altogether clear The great convenience of intravenous administration of barbiturates has spurred their widespread use in emergency surgery Seeley et al. (73) observed that barbiturates inhibit lymph flow and these accordingly might be regarded as a useful agent against the further depletion of blood volume. Beecher *et al.* (6) subsequently confirmed this finding in burns and suggested the possible usefulness of barbiturates for this purpose Many investigators have been impressed by the rapid precipitation of the shock state in depleted, malnourished, or traumatized animals by the administration of barbiturates The counterbalancing effect of barbiturates upon oozing surfaces offers small compensation against this hazard in deep shock. The experimental data which confirm the clinical experience are (*1*) Hemorrhagic shock in dogs receiving no medication whatever may be reversible to transfusion even after a number of hours of severe hypotension. (*2*) If barbiturates are given especially after the shock has persisted for some hours irreversibility to transfusion is very likely to follow (*3*) A tourniquet applied to the leg of a dog for 5 hours will not induce deep shock, but if barbiturates are given, fatal shock will result. The survival rate of nembutalized rabbits in tourniquet shock is half that of non nembutalized rabbits in tourniquet shock. (*4*) The shock produced by continuous administration of adrenalin is not fatal unless the animal is under nembutal. (*5*) Microscopy of peripheral flow in the exteriorized omentum of the dog in shock demonstrates the rapid onset of peripheral stagnation and loss of tone in terminal arterioles immediately after the administration of barbiturates (93) This effect is even more intense when ether is used Cyclopropane does not influence peripheral flow, and morphine affects it very slightly, though adversely

Blalock and Mason (10) found the tolerance to bleeding to be unaltered by morphine An extensive series of dogs which received a single dose of morphine (2–3 mg./kg.) before the induction of shock, showed no noticeably harmful effects as compared to dogs under barbiturates (24a)

The damage to tissue function from anesthetics appears to be inflicted indirectly i.e., by aggravating the crippled state of the peripheral circulation, although a direct tissue effect is suggested by the observation of Meyer and Potter (52) that nembutal decreases the uptake of oxygen and phosphate in tissue extracts

Intermediary Metabolism

Since the problem in shock irreversible to transfusion is one of restoring volume and velocity of flow through peripheral vessels and since all efforts to correct the hemodynamic failure by a variety of methods calculated to influence the circulatory apparatus have not succeeded it is natural to consider the biochemical disorder directly The nature of the disorder is obscure and has received close attention in the last few years These studies are largely concerned with the effects of anoxia on individual organs on intermediary metabolites and on the enzyme systems involved in their disintegration. The disturbances in individual organs excepting liver cannot be implicated on the available evidence as being important contributors to the prevailing general disorder The existence of widespread cellular disturbance is evident from the increase in the blood levels of pyruvic, lactic and amino acids the dephosphorylation of cocarboxylase the acidosis and the decline in oxygen consumption and the basal metabolic rate. Meyer and Potter (52) attribute shock to a faster breakdown than resynthesis of adenosine triphosphate, with the result that the oxidation of pyruvic acid by phosphorylation (the limiting reaction in shock) to yield energy and CO_2 is defective In shock produced in rats by the Noble-Collip drum or by tourniquets, they observed a rise in the blood concentration of inorganic phosphate, and pentose, lactic and pyruvic acids. They interpreted these changes as evidence of depletion of the energy reservoir in tissues i.e., depletion of adenosine triphosphate phosphocreatine and glycogen, all of which appeared to be diminished especially in the liver and kidney on direct analysis of tissues from shocked animals Rats

conditioned against drum shock did not show these changes on exposure to an ordinarily fatal degree of drum trauma.

Shorr (77) studied the effect of anoxia in tissues in vitro He found a decline in glucose, creatine phosphate, and adenosine diphosphate, and a rise in inorganic phosphate, but anoxia of 2 hours duration was not sufficient to permanently destroy the contractility of smooth muscle. Engel *et al.* (23a–b) observed a rise in blood amino nitrogen following occlusion of circulation of the liver Liver slices from rats in which blood flow to the liver has been occluded or from rats in hemorrhagic shock, show a deficiency in the synthesis of urea from ammonia in proportion to the duration or degree of anoxemia. Because the increases in ammonia nitrogen and in amino nitrogen in liver tissue run parallel, it appears that the liver loses its ability to deaminate amino acids together with its ability to synthesize urea. The increase in the amino acid level in the blood suggests an increase in protein breakdown, derived in part at least from the liver Rats fed with a high protein diet are more resistant than fasting rats to occlusion of blood flow to the liver Rats fed with a low protein, high glycogen diet are less resistant than fasted rats Seligman *et al* (78b) studied the blood glucose, lactic, pyruvic, and amino acid curves in progressive hemorrhagic shock, and the effect of the intravenous administration of these substances and of blood transfusion upon their blood levels. In the presence of elevated blood pyruvate and lactate injected pyruvate or lactate was readily metabolized, no matter how advanced the shock state was Amino acids were deaminated in all phases of shock, including irreversible shock not responsive to transfusion. While Engel *et al.* (23a–b) found a correlation between the amino acid level and irreversibility to transfusion in mice in hemorrhagic shock, Seligman *et al.* found no close correlation between this level or of the lactic-pyruvic acid ratio and the response to transfusion. Increased levels of these acids, moreover, are not a specific manifestation of shock Such increases occur in fever in the absence of shock, during muscular activity in adrenalin infusion, and in other conditions The increase in the lactic–pyruvic acid ratio appears to be due to an increased rate of glycolysis rather than to a deficient catabolic mechanism. The adrenal gland bears no specific relationship to these changes, since they also occur in adrenalectomized animals in hemorrhagic shock.

Glucose tolerance is defective in hemorrhagic shock, and its clearance from the blood is better after than before transfusion, but the customary fall in the lactic acid level after transfusion is not influenced by the injection of glucose. The deficient clearance of glucose may be due not to severe liver damage, but to poor blood flow through the liver, since after transfusion the clearance of glucose is adequate.

The rise in the lactic pyruvic acid ratio and in the amino acid level is explained by Engel (23c) as due to failure of the deaminating enzyme system in the liver This is doubtful, since the blood is readily cleared of injected individual amino acids (glycine, ala nine, aspartic acid cystine, and tyrosine)

LIVER PERFUSION

While there is no precise correlation between any observed feature in the biochemical disorder and the development of irreversibility to transfusion, there is evidence to implicate the liver as a controlling factor in the situation. (23a–c 78,82) The liver receives much of its blood supply from the portal vein, which in shock has a much reduced volume flow of blood with a very low oxygen content.

Experiments aimed at preserving the integrity of the liver while the remainder of the organism is exposed to the general effects of the shock state were devised (35) The splenic vein of a healthy dog is prepared some days in advance for cannulation. Hemorrhagic shock is induced. One carotid artery of a donor dog is connected to the splenic vein of the dog in shock. Both femoral arteries of the dog in shock are connected to one femoral vein of the donor Calibrated manometers constructed on the Bernouille principle are introduced in the delivery and return circuits. Both dogs and the entire connecting systems are heparinized. When the dog in shock has been bled so that the blood pressure has been stabilized at a level of some 30 mm. Hg, all circuits are opened and the shocked dog receives through the splenic vein some 350 to 450 cc. of arterial blood per minute from the donor dog. This volume flow of blood approximates the portal flow through the liver in a normal dog (10) Volume flow to, and return from, the dog in shock is controllable and is readily equalized by adjustable clamps on the connecting tubes so that over

a period of hours no measurable difference between volume of delivery and return is observed

Experience has demonstrated that nearly all dogs in hemorrhagic shock maintained at a pressure of 30 mm. Hg for 1.5 to 3 hours will be unresponsive to transfusion. As explained above, such dogs connected to an elevated bottle containing the shed blood will begin to take blood back from this reservoir as they approach the state of rapid collapse When they have taken from one-third to one-half of the shed blood volume, well over 90 per cent will show no sustained response following the rapid reinfusion of the remainder The taking-up process, therefore, may be used as an almost unfailing sign of the existence of irreversibility In viviperfusion experiments, the dog in shock, as soon as its blood pressure begins to give way, takes up from the donor dog, which like the elevated bottle, acts as a supply reservoir This is registered in terms of a decline in donor blood pressure and is measured approximately by noting the amount of blood, taken in advance from a third dog, which is required to return the donor blood pressure to its original level When one-third to one-half of the shocked dog's shed blood volume has been taken up from the donor dog, the dog in shock is regarded as probably irreversible. At this point, the cross circuits are closed and disconnected and the dog in shock is then given back all the shed blood. Nothing further is done. Post transfusion observations are made, and survival time is observed.

The same technic was used in a control group of dogs in whom the jugular instead of the splenic vein was used as the route for viviperfusion.

The liver perfused and jugular perfused dogs showed a remarkable difference in response to viviperfusion. The liver perfused dogs showed progressive improvement in alertness and strength return of restlessness, and a permanently sustained blood pressure. They were able to stand and drink water All but 1 of 14 went on to recovery All but 2 of 17 jugular perfused dogs declined precipitously and died early, with the same manifestations as dogs in irreversible hemorrhagic shock who are not cross circulated. All donor dogs in all experiments survived without injury

Disturbances in intermediary metabolism were less marked in shocked dogs being viviperfused, as compared to shocked dogs not

perfused. There was no evidence, however, that survival of the liver perfused dogs bears any relation to the lesser degree of metabolic derangement.

Anoxia of organs or tissues other than liver does not appear to be important in the development of irreversibility in hemorrhagic shock, since viviperfusion of the liver provides sufficient protection to produce survival, while viviperfusion through the systemic veins does not. It is not possible to say whether maintenance of liver integrity protects by preventing secondary deterioration in tissues other than the peripheral vascular system

These observations indicate that loss of liver integrity is a significant factor in the collapse of the organism in advanced hemorrhagic shock and that the preservation of liver function is of crucial importance in recovery from advanced hemorrhagic shock.

For therapeutic purposes it is more appropriate to observe whether the irreversibility to transfusion can be allowed to occur before perfusing the liver The existing problem in traumatic shock is not what to do while fluid therapy is still completely curative, but what to do when available therapeutic procedures have been applied and have failed—that is to say presumably when the liver has already suffered a degree of damage from prolonged anoxia which is likely to be fatal. Accordingly in a subsequent series of experiments viviperfusion was not started until the taking up process was in full swing and transfusion was shown to have failed. As cross circulation proceeded, the liver perfused dogs stopped taking up within $^1/_2$ to 1 hour after starting the perfusion, indicating recovery of peripheral tone, but the jugular perfused dogs did not stop taking-up, and died as rapidly as unperfused dogs after transfusion. The slowing up and the final halting of the taking up process in the liver perfused dogs is a dramatic visualization of the relation of the liver to recovery and maintenance of tone in the peripheral vascular system. The results were similar to those of the first series, i.e., survival in 8 of 9 liver perfused dogs and death in 7 of 9 jugular perfused dogs.

The prevention of irreversibility or its cure by viviperfusion of the liver demonstrates once more the all pervading importance of normal liver function. It is apparent that the extreme damage suffered by the anoxic liver is not an irreversible reaction. It remains

to be considered whether the contribution of the donor animal represents merely a better supply of oxygen to the liver or something more by way of protective substances present in normal, fully oxygenated arterial blood. If we assume the latter to be the case we must also assume that such substances are not useful to the organism unless they are delivered directly to the portal system, otherwise jugular vein perfusion should be equally protective. Such an assumption is too remote a possibility, especially since the production of a total Eck fistula is compatible with good health. The donor animal's protective role seems not to consist in the provision of depressor neutralising substances, because the control animal should show improvement in the taking up phenomenon in the same way as the liver perfused dog, at least while the cross circulation proceeds. From the available evidence, it seems that the donor's contribution consists solely in a supply of arterial blood in sufficient volume and for a sufficient time to enable the recipient's liver to restore a factor essential to maintain integrity of the peripheral vascular mechanism.

The findings of Shorr *et al.* (78) in some respects are in striking agreement with ours. From their observations they advance the concept that the peripheral vascular mechanism *fails* because of a circulating depressor material elaborated by the anoxic liver There is, however, one important deficiency in their findings to sustain this concept, to wit the depressor substance has been found only in shocked dogs which are under the influence of barbiturates. Our own data do not disclose the presence of a positive noxious agent. It is as correct to infer from our data that the collapse of the peripheral vascular mechanism is due to the absence of a protective or sustaining factor in the liver

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Strictures of the Common Bile Duct

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Introduction

Strictures of the common bile duct are very serious lesions. They deserve most careful consideration, not only because the results of their repair have been so unsatisfactory, but particularly because in most cases they are preventable It is true that sometimes oper ative repair is rather simple, and is followed by relatively good results but more often repair is difficult, and final results are com paratively poor The many improvements developed in recent years give hope that a truly satisfactory method of repairing strictures of the comon duct will eventually be discovered.

The fact that results are remarkably good for a year or two after almost all types of reasonably accurate repair is misleading. It is only after the lapse of this period that recurrences frequently develop although obviously the results are better after some operations than after others. However when there is no recurrence 2 to 2½ years after operative repair of a stricture, the relief may last indefinitely except when an implanted tube becomes plugged Nevertheless recurrences have occurred even after this period.

The condition is relatively common. It is most frequently observed in the large teaching clinics, where patients with stricture of the common duct are apt to gravitate. At the Mayo Clinic for example, in the 10 years between 1933 and 1942 Flickinger and Masson (31) reported 218 operations in 188 cases of benign stricture of the common bile duct. In the Illinois Research and Educational Hospital, we encountered 39* such strictures during the past 10 years (1937–

* The data on 10 additional cases encountered during the year elapsing since the data in this report was compiled has not been included because results cannot be analyzed in strictures until at least one year has elapsed since repair

1947), and 53 reparative operations were performed upon these patients.

Etiology

The possible causes of benign strictures of the common bile duct are (*1*) operative trauma, (*2*) inflammation (obliterative cholangitis), which may be related to cholangitis, pylephlebitis, abscess, or collection of bile about the duct (*3*) *secondary to pancreatitis*, (*4*) ulceration due to gallstones (*5*) tumors and multiple cysts. Without exception, all *investigators* have been *impressed with* the fact that most strictures of the common duct are secondary to trauma occurring *during operations on the biliary system*. This trauma may be caused by (*a*) excision, in the belief that it is the cystic duct which is being excised (*b*) ligation usually with a bleeding vessel (*c*) too close ligature of a cystic duct (*d*) gastrectomy (*e*) rarely following choledochostomy

In our series of cases (see Table I, page 127), we were able to show that at least 64 per cent of the strictures were unquestionably produced by operative trauma. An additional 20 per cent developed jaundice from 4 months to 5 years following cholecystectomy In 13 per cent of our series, the stricture was caused by chronic sclerosing pancreatitis.

In Flickinger and Masson s series of 188 cases (31), cholecystectomy had previously been performed in 96 per cent, cholecystostomy in only 3 per cent, and only 1 per cent had had no operative intervention on the biliary system. Approximately 17 per cent had had a choledochostomy although only half of these had immediate symptoms after operation. From their study they concluded that 73 per cent of benign strictures appear to be the result of surgical accident. Other authors estimate an even higher figure, for example, Cattell (13d) gives 80 per cent.

Direct injury to the duct may be sustained in many ways. Perhaps the most frequent injury is actual excision of a portion of the common duct along with the cystic duct. When the surgeon grasps the gallbladder, retracting upward for exposure, the common duct is put under tension. This may produce a Y angulation of the common duct, if this is incompletely seen, it can be mistaken for the cystic duct and a clamp may be applied (Fig. 1) This error is most readily

made when the cystic duct is short and thick, and the common duct is mobile (Fig. 9) Even if the specimen is inspected after operation no remnant of the common duct may be found particularly when the clamp grasps the common duct at its junction with the cystic duct, under such a circumstance the cystic duct may be cut flush with the common duct, which is included in the clamp, and obstructed with the ligature.

Stricture may be produced as a result of attempts to stop hemorrhage from the cystic artery which may have torn lose from an artery forceps or may have been cut before clamping. If the surgeon begins to stab blindly into the blood filled area, he may ultimately catch the bleeding point, but frequently a portion of the common duct will also be caught with the clamp This is particularly true when the field is blood-stained or blood filled, making identification of structures difficult. Another source of injury is in the anomalous crossing of the right branch of the hepatic artery anteriorly to the common hepatic duct (Fig. 10) or when from its position posterior to the common duct it courses anteriorly alongside the cystic duct (Fig. 11) The resultant hemorrhage obscures the operative field, and during its control the common duct is apt to be damaged or caught in a ligature. By the same mechanism, an accessory cystic or right hepatic artery (Fig. 12) may be responsible for injury to the common duct.

In some cases the common duct may be injured in the absence of hemorrhage. For example, the common hepatic duct not infrequently curves sharply to the right and anteriorly in its upward course toward the liver, and thus may lie in close proximity to the proximal portion of the cystic duct, particularly if the latter structure is long and tortuous careless dissection of the cystic duct under such circumstances may result in damage to the common hepatic duct. On other occasions, the attempt to ligate the cystic duct close to the common duct may result in constriction of the common duct by the ligature applied to the stump of the cystic duct. Practically all of these errors are the direct result of carelessness or haste, although lack of accurate anatomic knowledge may be an important accessory factor

In extracting stones from the common duct, particularly from its distal end, care must be taken to avoid trauma to the duct, for such trauma leads to the deposition of fibrous tissue, with consequent

stenosis Occasionally a large stone actually causes ulceration through the wall of the common duct, when the stone is removed the scar formation following healing may produce a stricture

Strictures rarely form at the site of a choledochostomy but it seems obvious that tearing of the duct, devascularisation by crushing with a forceps, or excessive manipulation, can cause formation of a stricture

In a small number of cases the mechanism of the stricture formation is not clear, as the symptoms may not develop for several months after operation. Thus Flickinger and Masson (31) noted that in 12 per cent of their patients *symptoms began to appear 1 to* 10 months after cholecystectomy, the average being 5 months. In *our own series, 14 per cent of the patients were symptomless for 4* months to 5 years following operation. The lesions in these patients *might be designated as obliterative cholangitis although it may not* be possible to obtain a history of acute suppurative cholangitis Sometimes it seems likely that a small abscess might have formed over the duct and produced enough scar tissue in resolving to stenose the duct. Any inflammatory process adjacent to the common duct, such as pylephlebitis may give rise to an inflammation which will ultimately produce a fibrosis of the duct. The authors firmly believe that extravasation of bile is a common cause of stricture, and particularly of its extension, since leakage of bile is commonly associated with surgery of the duct. It is even conceivable that in certain cases no actual trauma was inflicted on the common duct, nevertheless, if an appreciable quantity of bile collects over the common duct because an accessory hepatic duct has been sectioned or because a ligature on the cystic duct has slipped the resultant inflammation might give rise to a stricture Bile is known to be very irritating to the peritoneum since infection of the wall of the common duct may also be present, the infection superimposed on the inflammation created by the collection of bile might, understandably give rise to a process which would actually destroy the wall of the common *duct. Such a process might explain the* development of some of the strictures which develop several months after operation

Tumors and cysts may produce partial or total obstruction but are obviously not related to inflammation, discussion of these lesions is not *included in this report.*

Prevention of Strictures

Since the majority of strictures are secondary to trauma, every possible precaution must be taken to prevent technical accidents The surgeon must develop the policy of constant care and of exact dissection. Haste is never excusable in dissection about the bile

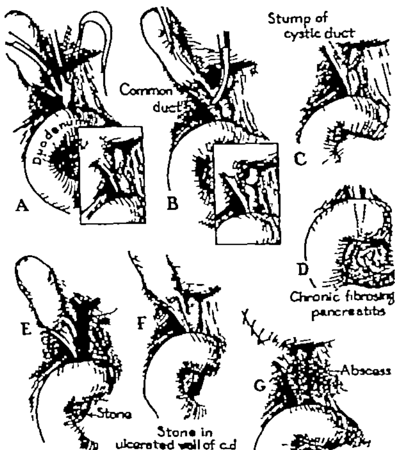


Fig. 1. Mechanisms involved in the production of stricture of the common duct (17a) A, Partial ligation of the duct while controlling hemorrhage. B, If there is undue traction on the gallbladder a mobile and inadequately exposed common duct may be mistaken for the cystic duct and ligated. C, Ligation of the cystic duct too close to the common duct. D Chronic, diffuse, fibrosing pancreatitis. E, Neglected suppurative cholangitis F Ulceration of the wall of the common duct by a stone. G, Progressive fibrosis of the duct following resolution of an abscess or collection of bile.

ducts, not only are there numerous vital structures in this area, but anomalies as well are very common. Good exposure must be obtained even though the incision must be lengthened considerably to obtain it. The cystic duct and the cystic artery must be separately isolated and individually tied. No structure should be cut until it is identified this is particularly true when the cystic duct is being dissected The common duct must be isolated and identified before a clamp is

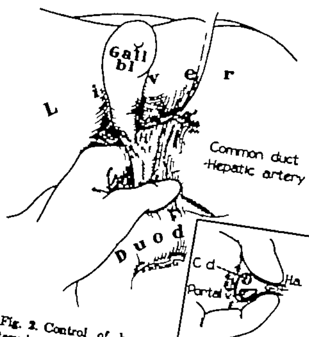


Fig. 2. Control of hemorrhage from the cystic artery by compression of the hepatic artery between the thumb and index finger with the latter inserted in the foramen of Winslow (17a)

placed on the cystic duct. No blood vessel should be ligated in the belief that it is the cystic artery until it can be proved that the vessel actually enters the gallbladder wall. Dissection in this area calls not only for a knowledge of the anatomy but of the many anomalies as well. The surgeon must use his eyes as well as his brain and his hands. Perhaps the emphasis placed on ligation of the cystic duct close to the common duct has been too great, for if this rule is followed too literally there is no doubt that occasionally the common duct will be pinched by the cystic duct ligature.

Sudden hemorrhage deep in the wound is usually due to injury of the right hepatic artery or failure to secure the cystic artery In jury of the portal vein is apt to occur only during the repair of stric tures In this circumstance the common duct, which normally should lie anterior to the vein, thus protecting it from injury, may be absent. Blind stabbing with an artery forceps in the neighborhood of the bleeding point must be avoided when bleeding arises from either of the two arteries. Control of the hemorrhage should be attempted by inserting the index finger in the foramen of Winslow and com pressing the hepatic artery in the hepatoduodenal ligament against the thumb (Fig. 2) After the bleeding is thus controlled, the vessel may be released slightly and the actual stump of the vessel may then be found thereby eliminating possible damage to the common duct with artery clamps.

When dense adhesions are present about the common duct, the surgeon in dissecting the structures about it, must be mindful of the fact that the ampulla of the gallbladder, particularly the portion known as Hartmann's pouch (Fig. 5) may actually be adherent to the common duct.

Anatomy of the Biliary Tract

The majority of common duct strictures result from operative trauma inflicted during cholecystectomy Although carelessness and haste are instrumental anomalies play a very important role in such accidental injury and that is why great familiarity with the anatomy of the biliary tract is essential (Figs. 3 and 4) Indeed, nowhere else in the body are anomalies so common. Anatomic variations are found so often in this region that it is difficult to establish a norm for these structures. One may fairly and accurately say that the so-called normal represents an average of the more common types observed. An illustration of such an average of types encountered by us in the operating room and in about 100 fresh and preserved cadavers is presented in Figure 3

Gallbladder

The anatomic relations of the fundus or dome of the gallblad der to the formation of common duct strictures is of little signifi cance, although the colon, which usually lies in contact with the gall

bladder, may be injured during cholecystectomy, particularly when adhesions are present. On the other hand, the anatomic relations of the neck of the gallbladder are important in the causation of stric tures. Frequently a sacculation of the neck of the gallbladder (Hartmann s pouch) projects so far posteriorly that it lies against the common duct (Fig. 5), in cholecystitis it is commonly adherent, so that in isolating the neck of the gallbladder the duct may be in jured if dissection is carelessly done.

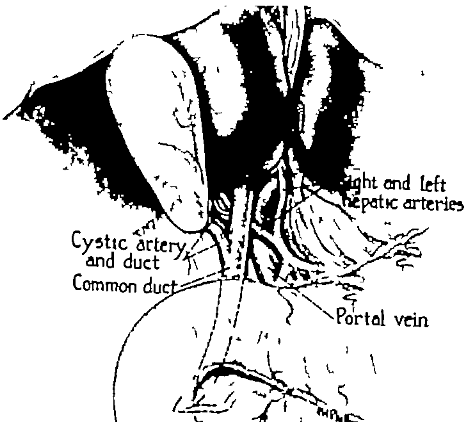
Bile Ducts

Cystic Duct The neck of the gallbladder terminates in the cystic duct, which normally is 3 to 4 cm. long and quite tortuous It joins the common hepatic duct to form the common bile duct 1 to 2 cm. above the superior border of the duodenum.

In 2 to 5 per cent of patients the cystic duct is large but short, so that it is difficult to identify the junction of cystic and common ducts (*Fig 6*) *In such cases, the common duct may be confused with the* cystic and be damaged by application of clamps or actually partly excised along with the gallbladder and cystic duct. In 20 to 25 per cent of patients (27a) the cystic duct is long and closely adherent to the common duct, or may actually curl around it (Fig. 7) It may enter the common duct as low as the pancreatic portion If separa tion of the cystic from the common duct is attempted carelessly and too vigorously the latter may be damaged. Although the trauma may not appear to have been severe, there is some evidence to support the belief that stricture may result even from such trauma weeks or months after operation.

Hepatic and Common Ducts In about 90 per cent of cases, the right and left intrahepatic ducts join within the liver substance to form the *common hepatic ducts while in the remaining 10 per cent* the junc tion takes place outside the liver In about 15 per cent of autopsy specimens (32) an accessory hepatic duct is encountered, arising from the right lobe of the liver and joining the common hepatic duct at various levels (Fig 8) and less commonly a small accessory duct empties directly into the gallbladder from the adjacent liver If the accessory duct is not ligated when severed during cholecystectomy drainage from the cut end may give rise to bile peritonitis and produce inflammation *in the region of the common* duct, with resultant stricture formation.

Figures 3 through 19 which follow are from the motion picture "Anomalies of the Bile Duct and Blood Vessels Strictures of the Common Duct" and are printed here through the courtesy of the American College of Surgeons



ight and left
hepatic arteries
Cystic artery
and duct
Common duct
Portal vein

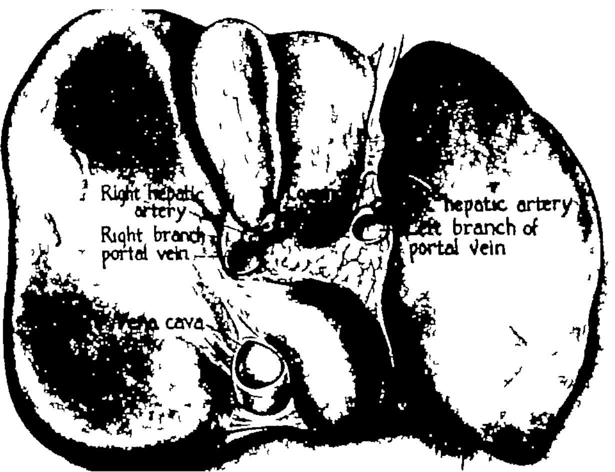

Right hepatic artery
Right branch portal vein
cava
hepatic artery
branch of portal vein



Fig 5 Unusually large pendulous Hartmann's pouch *Danger* Injury to common duct during dissection of adhesions between *the 2 structures.*



Fig 6 Short cystic duct, occurring in about 5 per cent of cases. *Danger* Injury to the common duct during *ligation of the cystic duct.*



Fig 7 A long cystic duct, adherent to or spiraling around the common duct According to Eisendrath (77a) this occurs in about 20 per cent of the cases. *Danger* Injury to the com



Fig 8 A accessory hepatic duct; in about 15 per cent of cases according to Flint (32) *Danger* If duct is cut and left unligated during cholecystectomy fibrous and tenosis (ommon



Fig. 9 An unusually mobile common duct. *Danger* Undue traction on the gallbladder may so distort the position of the duct that it is clamped and ligated in the belief that it is the cystic duct.



Fig. 10 Right hepatic artery crossing anteriorly to common duct in 12 per cent of cases, according to Eisendrath (27a) *Danger* Accidental injury of common duct during control of hemorrhage from anomalous artery

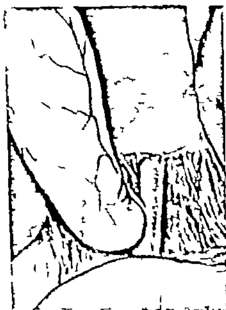


Fig 11 Right hepatic artery adjacent and parallel to cystic duct in



Fig. 12 An accessory cystic artery *Danger* Injury to the common duct

Occasionally the common hepatic duct is unusually mobile and projects to the right as it courses from the superior margin of the duodenum toward the liver Here again careless dissection of the cystic and common ducts sets the stage for damage to the common hepatic duct and perhaps even ligation.

Congenital atresia of the common duct is rare, it is seen only in infancy since this anomaly is usually fatal within a few months of birth unless corrected by operation. The condition is discussed in detail on page 145

Blood Vessels

Anomalies of the arteries are perhaps a more frequent cause of stricture formation than anomalies of the ducts operative trauma probably occurring most commonly during control of accidental hemorrhage in the region of the common duct.

Although the right hepatic branch arises normally from the main hepatic artery Flint (32) noted that it was derived from the superior mesenteric artery in 21 per cent of cases rarely, it may also arise from the aorta, or renal gastric, or superior mesenteric arteries. In 4.5 per cent of cases, he found an accessory right hepatic artery usually arising from the superior mesenteric artery In 12 per cent of autopsy specimens Eisendrath (27a) noted that the right hepatic artery crosses to the right, anteriorly to the common duct instead of posteriorly (Fig. 10) In our experience in operations for lesions of the biliary tract the right hepatic artery after leaving its normal position under the common duct, projects far to the right and anteriorly in about 20 per cent of cases it thus lies close to the cystic duct and in such a position as to be readily injured during dissection of this duct (Fig. 11) The cystic artery which according to Flint (32) arises from the right hepatic artery in fully 95 per cent of cases, usually courses toward the gallbladder posterior to the common hepatic duct, but in about 16 per cent of cases it crosses anteriorly to the duct. In about 15 per cent of autopsies he noted an accessory cystic artery which invariably crossed in front of the bile ducts it is likely to be divided particularly if the surgeon has already tied one cystic artery and is therefore not expecting another vessel in that immediate area (Fig. 12) The accessory cystic artery usually arises from the right hepatic artery but may be derived from the gastroduodenal artery In about 20 per cent of cases (27a) the

gastroduodenal artery lies anterior to the retroduodenal portion of the common duct.

Perhaps the most common arterial anomaly is the presence of a small artery in the anterior wall of the common duct, it is commonly severed when the common *duct is opened, but the resultant hemorrhage* is readily controlled. This vessel arises from the hepatic or gastroduodenal artery, and is present in about half of the patients operated on for common duct lesions

The portal vein lies posterior and to the left of the common duct and the hepatic artery These structures, along with lymphatics and nerves, are enclosed in peritoneum. In about 90 per cent of cases, the portal vein bifurcates before it enters the liver, in the remainder it enters as one major branch. The left branch of the portal vein enters the liver in the umbilical fissure at a point between the caudate and quadrate lobes The right branch enters the liver fully 2 inches to *the right of the left branch and ½ to 1 inch posterior (Fig. 4)* The right and left hepatic arteries usually enter the liver at a point near *and slightly anterior to the entrance of the respective branches of the* portal veins.

The common duct enters the liver at a point about midway between the entrance of the two branches of the portal veins, but *slightly anterior to a line drawn* between the entrance of the two veins (Fig. 4)

It is essential that the surgeon operating on patients with strictures of the common duct have accurate knowledge of these structures in the hepatoduodenal ligament, and the relationship of the various structures entering the liver because adhesions are usually so dense that the anatomic architecture is almost totally obscured. In general the location of the portal vein, as demonstrated by hypodermic needle (page 104), will be a helpful guide in searching for stumps of the common duct.

Diagnosis of Stricture

With very few exceptions, evidence of jaundice and biliary fistula will develop three to four days after operation *if the common duct* has been obstructed by any of the operative procedures, either one should arouse suspicion of trauma of *the common duct*, although they are by no means positive evidence that such an injury has occurred *Careful examination of the gallbladder specimen* for a

segment of common duct should be made in all cases after removal of the gallbladder The jaundice might be caused by ligation of the ductus choledochus by hepatitis by collection of bile within the peritoneal cavity or by absorption of blood from a large hematoma. A biliary fistula might result from transection of an accessory hepatic duct or the slipping of a ligature from the stump of the cystic duct If the possibility of injury to the common duct is great the patient should be operated upon immediately

The signs and symptoms of common duct stricture are jaundice pain, pruritus acholic stools chills and fever If jaundice or a biliary fistula develops within a few days after cholecystectomy injury can often be diagnosed with certainty But if the jaundice appears many weeks or months after operation other etiologic factors as well must be reckoned with. Three major possible explanations must be considered in attempting a specific diagnosis (*1*) stone in the common duct (*2*) carcinoma of the pancreas or ampulla of Vater (*3*) traumatic or inflammatory stricture of the common duct

Ordinarily the pain is greater when the obstruction is caused by a stone in the common duct than in the other two conditions the pain being least with pancreatic carcinoma If obstruction is due to a stone or to a stricture the attacks of jaundice and acholic stools will almost invariably alternate with freedom from obstruction With carcinoma of the pancreas when jaundice once sets in it rarely disappears or even decreases in intensity except when the growth arises at the ampulla where sloughing of the tumor may decrease the jaundice temporarily and also give evidence of bleeding into the intestine Chills and fever are more usual with common duct stricture than with any other obstructive lesion indeed they are almost invariably present, although they may not appear until after the first few weeks of obstruction.

In making a differential diagnosis the patient s history is of course invaluable. Traumatic stricture can obviously be ruled out in the absence of previous operation, but the possibility of an inflammatory stricture still remains If jaundice develops in the absence of previous operation common duct stone can usually be differentiated from carcinoma of the pancreas by the presence or absence of pain. With few exceptions a patient whose duct is obstructed by a stone will have had characteristic symptoms particularly the pain of gallbladder disease The history of a difficult cholecystectomy with

Absence or Stricture of the Common Hepatic Duct. We encountered relatively few examples of this type of lesion (Fig 14c) in which the distal portion of the duct was of sufficient caliber to be used in an end-to-end anastomosis. In many cases the proximal

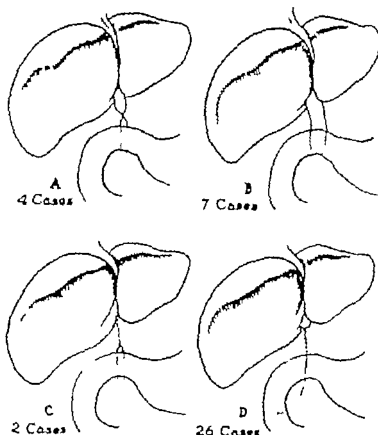


Fig. 14. Types of stricture of the common duct encountered in a series of cases (17d) A, Local stricture. B, Stricture of the distal end. C, Stricture or absence of the proximal duct. D Stricture or absence of the entire duct caused by trauma and obliterative cholangitis.

portion of the duct had probably been excised in others, a gradual obliterative process, *secondary to an inflammation, may have* caused the obstruction. The latter mechanism is unquestionably an important one the authors have encountered many *cords or remnants of* common hepatic duct with little or no evidence of damage by opera

tive trauma, but the lumens of which were too small to allow adequate passage of bile.

Absence or Stricture of the Common and Common Hepatic Ducts Accidental excision of the entire common and common hepatic ducts is practically impossible. However excision of a part of the common duct may be followed by atrophy of the remaining portion because of trauma devascularization or lack of function. We have encountered cases in which the supraduodenal portion of the duct was absent, but with a narrow common duct in the pancreatic portion the lumen of which was too small for transporting adequate quantities of bile In such cases it was clear that an inflammatory process perhaps secondary to the original factor which might have been trauma, bile peritonitis abscess or the like was destroying the remaining portion of the duct

Review of the Literature

The description and discussion of the various procedures that have proved important in the development of choledochoplasty has been arranged according to the following classification beginning with the most easily repaired defects

(*1*) End to-end anastomosis of a divided biliary duct, direct or indirect.

(*2*) Plastic reconstruction of a portion of the biliary tract by the use of a pedicle flap from the gallbladder or from the intestinal tract.

(*3*) Dilatation of a ductal stricture.

(*4*) Implantation of a biliary fistula into the intestinal tract.

(*5*) Implantation or anastomosis direct or indirect, of the common hepatic duct gallbladder or cystic duct into the intestinal tract.

(*6*) Establishment of continuity when there is loss of all extra hepatic biliary ducts

End-to-End Anastomosis of Divided Common Duct

This was first performed in 1892 by Doyen (25) for a defect made by a stone. The patient did not survive. Körte (55a) performed the same operation in 1898 his patient died on the thirteenth postoperative day as a result of hemorrhage from a gastric ulcer Both Doyen and Körte realized the importance of providing drainage for the

bile the former accomplished this by placing an indwelling catheter in the duct, the latter by decompressing the proximal duct and performing a cholecystoduodenostomy In 1899 Kehr (53a) repaired a defect in the choledochus but provided for the anticipated swelling at the suture line by leaving a small defect in the anastomosis. There was drainage for several weeks, after which the fistula healed and the patient was cured Voelcker (101), in 1911, introduced transduodenal drainage. He threaded the drainage tube from the hepatic duct through the anastomotic site and out through the ampulla, and brought the tube to the skin through the anterior wall of the duodenum after burying it in a cuff of duodenal wall. The tube was removed on the fifth postoperative day, and a fistula remained from which bile and duodenal contents drained A second such case was also reported

Kehr (53b) in 1913, and W J Mayo (64c) in 1916, used a T tube to splint this anastomosis with the long arm of the tube emerging from the duct at the site of the anastomosis. Later, Mayo (64d) added the feature of a longitudinal slit in the distal and therefore contracted end of the duct. Horgan (43a) in 1923, described an L-shaped rubber catheter the short arm of the L provided for the continuity of bile flow and the single arm allowed the tube to be introduced either above or below the site of anastomosis. In 1928 Moynihan (74b) using Mayo's longitudinal slit for both the proximal and distal ends of the duct, resorted to the use of two catheters the distal catheter could be passed into the duodenum. The value of this "duodenostomy tube" for alimentation and reintroduction of bile is obvious. Furthermore, Moynihan (74b) emphasized the great importance of avoiding tension, he advocated that the duodenum be mobilized and moved a few centimeters toward the liver before sutures were placed in the ducts Individual ingenuity was displayed by Mayo (64a–d) Körte (55b) Voelcker (101), Jacobson (48) Stetten (96), Downes (24) Hotchkiss (45), as well as many others. The failure to report end results in the early days perhaps reflects the fact that end results were not known. Douglas (23) reported a case in which a relapse occurred after several years of apparent cure operation revealed a recurrence of stricture at the site previously repaired

Where tension prevented the direct approximation of the ductal ends, substitute tissues particularly omentum were used to bridge

the gap (81) Several reports expressed the hope that by using a T tube, about the ends of which the short ducts were brought as close as possible, a regeneration of the intervening duct might result (6,16,30,33,53,54 65,82,100) In these cases, also, the follow up was too brief for any estimate of the rate of cure judging from the known tendency for strictures to recur after many months. Present opinion with regard to such procedures is that they do not adequately meet the requirements for successful permanent repair

Although the value of some sort of tubular prosthesis to support the line of anastomosis was appreciated by many surgeons years ago McArthur (65), in 1923 was the first to devise a method for maintaining the tube in place for a controlled length of time. He placed a rubber tube or catheter in the common duct, with one end extending above the suture line and the other extending distally through the sphincter of Oddi so that 3 to 4 inches protruded into the duodenum (Fig. 15) The tube was anchored in place by passing a silk suture through its wall at the level of the anastomosis, and bringing the suture out through the wound threaded through a narrow tube to prevent the intestinal loop from being damaged by cutting. The ends of the sutures were anchored outside the wound when passage of the tube in the common duct was desired the suture was cut from its attachment, and the rubber tube over the suture removed. Invariably the tube in the duct, together with the suture, passes out through the anus, provided the end of the tube protrudes into the lumen of the intestine, although the length of time may vary from 1 to 6 weeks. The principle is a sound one and is still being used by some surgeons (104a,b) The procedure can also be made use of for maintaining a tube in place when a defunctionalized loop of intestine is anastomosed to the stump of common duct.

Various types of tubes have been used or recommended for supporting the suture line. In the past few years, most surgeons have adopted the T tube to support the suture line in end to-end anastomosis. The use of vitallium and plastic tubes is discussed on pages 101 and 106

When there is an actual defect in the common duct, it may be extremely difficult to find either end of the duct. It is usually more difficult to find the distal end but if it is at all possible it should be isolated for anastomosis to the proximal end so that the *sphincter of* Oddi will be preserved for function Lahey (57b,f) years ago pointed

out the value of mobilizing the duodenum at the laterosuperior border when attempting to find the distal stump of duct. Cattell (13b,d) advised carrying this dissection still further, so "the posterior portion of the pancreatic head can be visualized. The anterior division of the superior duodenal artery can then be sectioned and the pancreas split so that the intrapancreatic portion of the common duct can be identified and dissected free for a distance of 2.5 to 5 cm. Care must be taken not to free the left side of the duct near the ampulla in order to avoid injury to the pancreatic duct. The mobility of the duct, head of the pancreas and duodenum which is thus obtained permits its approximation to a short hepatic duct stump at the hilus of the liver, and this can be accomplished without tension.

Plastic Reconstruction of a Portion of Common Duct

In a limited number of reports ingenious methods have been suggested for utilizing neighboring, mucosa lined structures to bridge a short defect in the duct. Occasionally this principle has been used to replace a total defect. Occasionally too it has been incorporated in operations designed to implant the proximal duct into the gastro-intestinal tract. The first reported operation of this nature was made by von Stubenrauch (97) in 1905 who formed a mucosa lined tube from the wall of the stomach and attached it to the duct, thus allowing bile to enter the stomach. The patient was reported to be well 6 months postoperatively Kehr (53b) encountered a case in which removal of common duct stones resulted in severance of the duct, with a 3 cm. defect. This was corrected by utilizing the still present cystic duct and gallbladder to form a flap which was turned downward and sewed into the deficient portion of the duct. An indwelling Nélaton catheter was used. Walton (105) in 1914 utilized the duodenal wall to bridge the gap between the hepatic duct and the duodenum the indwelling tube passing spontaneously on the eleventh day A similar procedure was used by others, Mayo (64d) and Moynihan (74b) varying the technic slightly, but the end result in all these cases is not given beyond a few months. Ginsburg and Speese (35) used posterior rectus sheath with peritoneum to bridge a defect about a T tube, stoppage of bile occurred necessitating a second operation in which an indwelling straight tube was placed

from above the stricture and out through the ampulla. The result was reported as satisfactory at the end of 4 months.

Experimental use of transplanted grafts (vein or fascia) showed that they were very likely to slough in the presence of any infection. Although such seemingly radical procedures as the use of an appendix have been suggested to our knowledge such procedures have not been attempted.

Longitudinal incision and transverse closure (Heineke-Mikulicz operation) and longitudinal incision with reconstruction over a rubber drainage tube have been reported. The former method may still be considered useful although it is infrequently applicable The descriptions of all such procedures mention the importance of prolonged presence of indwelling intraluminal catheters to maintain the new diameter of the duct until enough time has elapsed for the con tracture to stop (2,6,28,51a, 57a–g, 65a b 74a,b 104a, b)

Dilatation of Stricture

This procedure seems very rarely indicated. It was first done by Parkes (78) in 1885 the patient developing pain and a fistula within 3 months following the operation. In 1908 Volkmar (102) reported a case of Kehr's (quoted by Merk, 68) in which the common duct was dilated daily starting 2 weeks after an end to-end anastomosis had been performed.

In the reports of these cases it is to be noted that the fear of recurrence after dilatation prompted most of the surgeons to use the indwelling rubber tube for a longer or shorter period of time to splint the dilatation (18b,22,28,51a)

Implantation of Biliary Fistula into Intestinal Tract

Although external biliary fistulas tend to remain open, partial obstruction associated with chills and fever (suppurative cholan gitis) is usually present. This tendency toward development of a partial or complete obstruction in the sinus tract was not appreci ated at first. In 1902 Czernev (quoted by Merk, 68) implanted the fistulous tract into the intestine and anastomosed the gallbladder to the intestine.

Neither of these stomas was functioning at autopsy primarily because of the presence of a carcinoma in the proximal duct. Von

Stubenrauch (97) implanted a fistula of 2 months' duration into the stomach. Necrosis developed at the point of implantation requiring another reconstruction this was done by using a flap of stomach wall. In 1912, Mariani (62) implanted a fistula from the gallbladder to the skin into the stomach The first operation was not successful but a second one was satisfactory Roith (87a) in a patient with a similar fistula, in 1924 first injected the bile from the fistula into the stomach through a gastrostomy tube when the patient had improved sufficiently to be able to withstand operation, the fistula was implanted into the stomach The result was good at the end of 1 month

F T Murphy (quoted by Eliot, 28) telescoped a fistula into the distal end of the common duct in 1918 he believed that the duct remained open for 6 months but the patient eventually became jaundiced and died.

In the other cases reported the results are much the same. A patient of William, reported by Lahey (57a) in 1923 was well after 10 years this fistula however had formed after drainage of a liver cyst, and there is no positive evidence that the distal end of the common duct was not present and did not remain open. Collins (18a) Masson (63) Roeder (86) Lilienthal (60a) and St. John (88) reported satisfactory results for short periods of time in their cases Two cases were reported by Whipple (107a) the results in both were unsatisfactory One patient died of cholemia, the other of peritonitis as the result of a gastric fistula that had developed about the site of impaired circulation in the biliary fistula

Indirect implantation' is the term used for the method of establishing an internal biliary fistula when a hollow viscus is not approximated to the biliary duct and the bile is delivered to the gastrointestinal tract via a rubber catheter which bridges this gap Only one case of biliary fistula which was thus indirectly implanted has been reported (111) the patient was asymptomatic at the time of the report, but the length of time since repair was not given.

Implantation or Anastomosis of Common Hepatic Duct Gallbladder, or Cystic Duct into Intestinal Tract

For many years implantation of the common duct into the alimentary canal has been a popular operation for repair of a biliary fistula, although the recurrence rate of the stricture in this group is still high. The explanation of this recurrence may perhaps be that

the factors which govern permanently successful healing between the open end of the biliary tract and the gastrointestinal tract have not been sufficiently appreciated and emphasized in the past.

Anastomosis of the biliary and gastrointestinal tracts was first attempted in 1880 by von Winiwarter (109) for a malignancy of the head of the pancreas His operation was a very elaborate six stage procedure, and it is noteworthy that he first tried to perform a cholecystocolostomy but finally had to resort to cholecystenterostomy Kappeler (52a) was the next to perform such an operation also for malignancy A similar procedure was followed independently by Monastyrski (71) a Russian his patient died 2 months after operation and at autopsy the opening was found to be intact.

Robson (85c,d) in 1893 performed the first anastomosis between gallbladder and intestine for a benign stricture which followed a cholecystostomy He used a bone bobbin to maintain patency of the lumen, in a manner surprisingly like that of today The patient was well a year after operation. It was Monprofit (73a b) who in 1904 first reported the use of the Y method of anastomosis between the gallbladder and jejunum. In 1908 he reported through personal communications (73c) that Moynihan, Docqs Delagemere, and Dotgans had used his Y method.

Cholecystocolostomy This operation was unsuccessful when von Winiwarter (109) first did it, but Robson (85a b) performed the operation successfully for a benign stricture A fistula remained open for several weeks, but then closed spontaneously after which the patient was in normal health. Chavasse (14) in 1891 fearing closure of the opening, resorted to Senn s bone plates to maintain the opening in the stoma. Bile and feces, which drained externally soon disappeared, and after a month there was no further evidence of fistula.

Cholecystenterostomy In 1888 Bardenheuer (4) reported 2 cases in which he united the gallbladder to the duodenum by the use of rubber sutures. One patient died the other recovered No autopsy was obtained on the patient who died. The next year Terrier (99) performed a similar operation except that his procedure was an elaborate one, in which the gallbladder and the duodenum were securely connected and the opening between them made through a second aperture in the gallbladder wall. At the same time a short rubber tube was placed in the stoma without sutures The patient

recovered and was well 4 months postoperatively *having had only* one attack of fever and pain Murphy (75) used his button in 1892 the patient being relieved At exploratory laparotomy 6 months later the gallbladder was found firmly united to the duodenum Robson (85f) discarded the use of the Murphy button and the decalcified bone bobbin preferring an open anastomosis, because in one case the button was retained and in another the opening closed within a few months

The first cholecystogastrostomy was performed by Wickhoff and Angelberger (108) in 1892 They used an open anastomosis and all that is known is that their patient recovered In the same year Monod (72) used a Murphy button to effect a cholecystogastrostomy The patient died on the second postoperative day but saves the report The anastomosis held perfectly Kehr (53a) reported a satisfactory result 3 years after a similar procedure The indication for the operation was not given

Cholecystocholedochostomy In a rare procedure Wolff (112) repaired an operatively created defect of the choledochus by suturing the fundus of the gallbladder to the distal end of the common duct When Wolff reported the case in 1914 the patient had been well for 4½ years.

Lateral Cholodochoduodenostomy The first report of this procedure was that by Riedel (81) who performed the operation in 1888 the patient dying the next day Sprengel (94) performed his operation after Riedel but the case was reported before Riedel's The patient recovered. The indications for both operations were gallstones The procedure once shown to be feasible has been used repeatedly with success

Cystic Duct Implantation. Direct implantation of the cystic *duct into the duodenum was done by Robson (85a) in 1898. The* inflammation of the gallbladder fundus led him to prefer this site He also implanted the cystic duct into the hepatic flexure of the colon when recurrence of symptoms several months later required reoperation, but the patient died from an unobserved tear in the colon. The cystic duct was implanted into the jejunum and the duodenum by Robson and into the stomach by Kehr While some patients recovered and some did not the cause of death seemed not to have been related to the site of the anastomosis nor to the technic which was utilized in effecting it.

Establishment of Continuity When All Extrahepatic Ducts Are Lost

Direct Hepaticoduodenostomy and Hepaticogastrostomy Kehr (53a) was the first (1902) to use this procedure which restored the physiologic entrance of bile into the gastrointestinal tract in more normal fashion, but W J Mayo (64b) was the first to report it (1905) Mayo's patient lived 19 years Kehr's operation

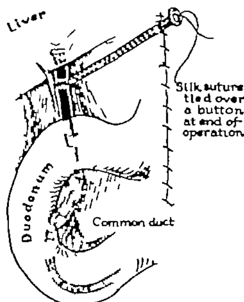


Fig. 15. McArthur method of anchoring a tube in the common duct. A silk suture is passed through the wall of the tube and threaded through a small rubber tube which is brought out through the wound or a small stab wound The ends of the suture are tied over a button or piece of sponge and cut when passage of the tube in the duct is desired.

was done for carcinoma of the common bile duct but no end result is given. To choledochoduodenostomy Voelcker (101) added an indwelling rubber tube which he exteriorized through a Witzel tube of duodenal wall the patient was discharged from the hospital in good condition on the fifth week. Mayo (64d) modified the technic of implantation of the common duct into the side of the duodenum by fashioning a flap of duodenal wall The results of their work extending over a period of 20 years were reported at intervals by them or their associates at the Mayo Clinic The end results were not entirely satisfactory although several patients lived for long periods of time As early as 1913 Samborsky (89) called attention to the danger of hemorrhage from injury to the portal vein, reporting a case in which the patient died. Fatal injury to the hepatic artery was reported by Enderlen (29) in 1908

Hepaticojejunostomy In 1908 Monprofit (73c) made use of his Y principle for creating an anastomosis with the interrupted duct as he had previously done for an anastomosis with the gallbladder Maingot (60c) reports a successful case so operated in 1932 *Dahl s patient (19) who was operated upon in 1909 was well 8* months later Lanphear (58) sutured the Y to the underside of the liver no attempt was made to effect mucosa to-mucosa junction and the results at the end of 2 months were adequate Jackson (47) used a loop of jejunum he cannulated the common duct with a rubber catheter which after traversing the wall of the jejunum by Witzel s method was introduced into the jejunum Satisfactory recovery was reported 6 months postoperatively at which time the fate of the tube was not known. Nordmann (77) utilized a similar technic performing a direct anastomosis between the common duct and the jejunum. He then brought the catheter back out of the wall of the jejunum to the abdominal wall which allowed removal of the tube at will. As previously described McArthur (65a b) anchored his catheter in place by the ingenious use of silk thread anchored to the abdominal wall with a button (Fig 15)

Indirect Implantation of the Biliary Tract. Many attempts have been made to create an indirect connection, by burying an indwelling prosthesis usually a rubber tube, in omentum, fascia or similar structure and allowing the bile to enter the intestinal tract via this indirect route Discarded today this method had considerable vogue in the first three decades of the present century Its adoption was based essentially upon the experimental work of Sullivan (98a b) which revealed that in the dog a bile duct will regenerate about a rubber drainage tube Cases were reported in 1910 by Jenckel (49) and Propping (82) in 1912 by Wilms (111) in 1914 by Mann (61) and more recently by Brin (11) Gernez (34) Hagyard (40) Brewer (8) Hagler (39) and McCorkle *et al* (66) The immediate postoperative course of such cases reveals an almost uniform relief of symptoms but most reports of the late results disclose a high recurrence rate.

Vitallium and Plastic Tubes. At the insistence of Walters (103a b) and others, mucosa to-mucosa anastomoses between the common duct and the intestinal tract have become an important part of plastic operations on the common duct, regardless of whether or not a tubular support is placed in the stoma. Walton s use of a flap of doudenum (105) and Lahey s use of the cystic duct (57b c)

were minor modifications The tendency of stenoses to recur (after apparently satisfactory anastomosis became increasin obvious as follow up observations were lengthened In an effor find a method of preventing such recurrences Pearse (80a) in 1 reported the use of a vitallium tube in 2 cases to bridge a defec the common duct, and Clute (15) reported its use in 1 case. Pe credits Zinninger with being the first to use a vitallium tube S that time, numerous workers have reported on the use of ingenious technic (5 12 13a,15,17d,26 41,60b,69,80a,87b,93,95) relative simplicity of the technic and its applicability to other quite insoluble technical problems explains why surgeons have be to use it increasingly That this method is not free of undesir complications is indicated by reports of encrustations within tube by Allen (1a) Whipple (107) Lord and Chenoweth (6 Seaman (93) Pearse (80e) and Cole *et al* (17d) Recently La (57g) reported satisfactory results with bouncing clay and Gr lay (37) is experimenting with polythene tubes.

Use of Mucosal Grafts to Prevent Strictures. In 1937 F (42) made use of a flap of gastric mucosa which he teased a from the surrounding serosa and muscularis to bridge a gap seemed to defy surgical correction. This procedure was also use McCurrich (67) in 1944 and by ourselves in a modified form.

In recent years even greater effort has been made to retain mucosa to-mucosa principle, in the hope of minimizing cicatriza of the duct at the hilus by covering the area with mucosa. Our mo cation of Hoag's procedure makes use of a defunctionalized (M profit Roux) loop of jejunum. As described in detail on page we construct a mucosal flap from the end of the jejunal arm insert it up into the cicatrized hilar duct over a rubber tube th sufficiently anchored to stay in place for several weeks

(2) Any departure from this principle for example the so-called indirect anastomosis using a *portion of fascia omentum, or some* other structure resulted in so high a rate of recurrence that such technics have now been abandoned.

(3) All permanent synthetic ductal prostheses so far tried have the tendency to become obstructed by a deposit of bile precipitates

(4) Anastomoses between the end of the biliary tract and a defunctionalized loop of intestine (e g Roux Y arm of jejunum) appear to heal with less tendency *toward recurrence of stricture* than when a functioning loop of intestine is used

(5) Any and all methods of repair are likely to give satisfactory results for the first few months

(6) Chills and fever due to suppurative cholangitis are more commonly the symptoms of common duct obstruction although regurgitation of intestinal contents in the absence of obstruction may give rise to these symptoms following operations allowing regurgitation of food into the intrahepatic ducts

(7) Anastomoses which involve the bile ducts should be splinted for 10 to 15 weeks with some form of internal hollow prosthesis which will maintain the patency of the biliary passage while the anastomotic line is healing. This is important for the edema associated with healing may frequently be so extensive as to compromise the ductal lumen Moreover the process of cicatrization usually continues for several weeks following any type of operation In our opinion maintenance of a lumen during this process of cicatrization will decrease the recurrence of stricture

Modern Methods of Repair of Strictures

Since the technic of repair of common duct strictures is usually extremely difficult and complicated it is natural that the development of successful methods has been slow A few very important facts have been learned from the vast experience of the past several decades (page 101) For example artificially constructed ducts will *not function longer than a few weeks or months* unless they are constructed of a structure lined with mucosa. Mucosa to-mucosa suture is therefore very important in constructing a duct but we have also learned that in the hands of many surgeons the simple anastomosis of the hilar duct to the adjacent intestine (i.e duodenum) utilizing this mucosa to-mucosa principle has resulted in a

very high percentage of failures a year or two following repair The poor results from this and other procedures in vogue 20 years or more ago have led to the development of various methods to be described in the following pages The technical difficulties encountered in these operations are frequently great. In general the massive adhesions which are so common in the right upper quadrant of patients with stricture constitute one of the greatest problems in the operation The use of an L shaped abdominal incision one limb being a right upper paramedian incision and the other directed to the right about the level of the umbilicus has helped insure good exposure. The adhesions may be so extensive that the free peritoneal cavity is not entered during the operative procedure The fact that these operative procedures are at times completely extraperitoneal may explain the surprisingly uncomplicated postoperative course which many of these patients experience. The density of the scar tissue and the distortion of anatomic relationships in secondary operations in this area often make good exposure extremely difficult to achieve.

The region of the common duct or hilus of the liver should always be approached from the right side, staying close to the liver during dissection (Fig. 16) This approach will minimize the likelihood of injury to the hepatic artery or to the portal vein since the common duct (if present) should lie between those structures and the area of dissection. Injury to the hepatic artery may be irremediable and result in death from liver necrosis within a few days However if the right hepatic artery has been severed and the error is detected before the abdomen is closed an attempt should be made to anastomose it Since the vessel is a small one, the procedure is difficult but a successful anastomosis was recently accomplished by Cattell (13e) Injury to the portal vein may be associated with such massive blood loss as to necessitate interruption of the operative procedure. As any delay may be fatal for a patient suffering from suppurative cholangitis such injury must be avoided In this area dissection must be carried out slowly (particularly when there is a possibility that the common duct is absent) so that any tear or incision in the portal vein will be small A small opening in the vein is readily repaired with one or two fine silk sutures whereas the massive hemorrhage resulting from a large opening requires a great deal of time for closure. The use of "gelfoam" for tears in the portal vein, as

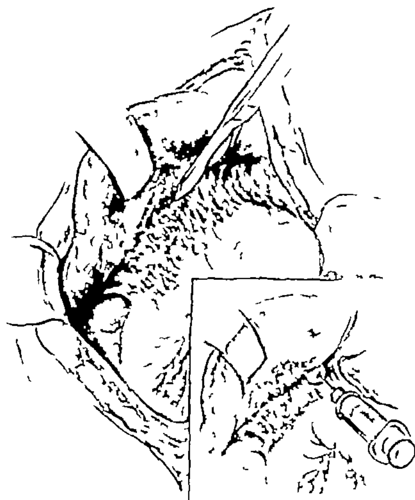


Fig 16 Exposure through dense adhesions (I"d) This is best achieved by dissecting between the liver and intestines with the knife or dissecting scissors starting from the lateral end If the duodenum has previously been attached to the stump of the duct at the hilus the bile duct will be encountered and opened before the portal vein or hepatic artery is reached. *Insert* Aspiration of hilar region to identify the duct stump from other structures.

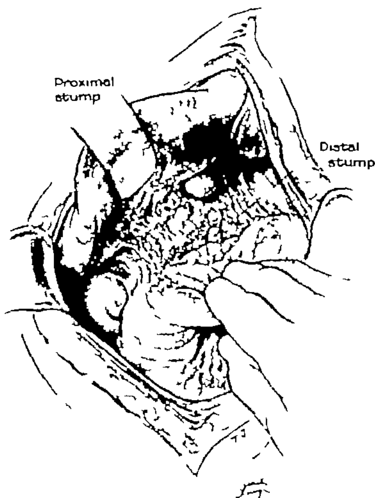


Fig. 1 Incision of the peritoneum laterally and superior to the duodenum with rotation of the duodenum and head of the pancreas toward the midline, will aid in finding the distal end of the common duct (17d) This should always be attempted, because of the great value of the sphincter of Oddi.

described by Jenkins and Clarke (50) may shorten the time required for repair of the damage

Even after the hilus of the liver is reached it may be difficult to locate the duct We have repeatedly had to extend our dissection up along an obliterated duct (represented only by a cord of fibrous tissue) until the dilated intrahepatic duct was found The use of a fine aspirating needle to ascertain the nature of structures whose gross characteristics are difficult to recognize because of scar has helped us to avoid injury to the portal vein The bleeding caused by puncturing the vein with a hypodermic needle stops promptly In practically all cases of obstruction, with complete absence of extra hepatic biliary tree bile can thus be obtained from the hilar region by aspiration However in 2 patients we were unable to obtain bile even though the entire area about the hilar region was aspirated at innumerable points A drain to the site of the aspiration was left inserted in the hope that a biliary fistula would develop The fistula did form and later was used as a guide to the dilated intrahepatic duct so that a definitive operation could be accomplished. The needle may have entered a dilated duct during our search but the contents were perhaps too thick to be aspirated with the size of the needle used In the presence of a pre-existing fistula the problem is considerably easier

As will be discussed later an extensive effort should be made to find the distal end of the common duct by incising the peritoneum on the lateroposterior border of the duodenum and rotating that organ medially (Fig 17) This maneuver will expose the edge of the head of the pancreas The distal end of the common duct may lie on the lateral surface of the pancreas but more commonly is located within the parenchyma of the pancreas This should be split in the attempt to find the distal duct (13a)

Local Resection and End to-End Anastomosis

When only a short portion of the common duct is involved in the stricture local resection and anastomosis of the two ends is the procedure of choice provided the two ends of the duct can be mobilized and brought together without tension (Fig 18) It must *be remembered that destruction of the duct s blood supply may* occur during mobilization of it ends The repair is made with inter rupted sutures either silk or catgut both of which possess certain

disadvantages If a silk suture extends through the entire wall into the lumen there is the possibility that concretions may be deposited on the suture which acts as a foreign body On the other hand more reaction is set up with catgut sutures Interrupted silk sutures appear preferable to catgut particularly if care is taken not to allow portions of the silk suture to extend through the lumen of the newly formed duct. Only a single row of sutures should be used when

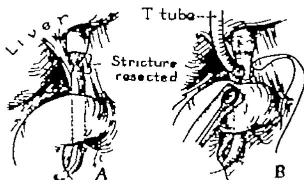


Fig 18 Repair of a local stricture (17a) A, Local stricture most commonly created by trauma. B After resection of the stricture a T tube is inserted above or below the junction of the two ends of the duct and the two ends are anastomosed with interrupted sutures.

approximating duct to duct a double row is apt to produce so much constriction that a secondary stricture will form. Even under these most favorable circumstances all details of the procedure must be carefully executed in order to prevent recurrence of the stricture. Insertion of a T tube one arm of which extends past the suture line will maintain patency of the lumen quite readily *The T tube must be inserted through an opening either proximal or distal to the suture line and not through the suture line* It should be left in place for at least 3 months, i e., until the healing and cicatricial process has come to a standstill The opening made for the T tube is closed around the tube and the tube is then brought out through the wound or through a stab wound, depending upon the location of the wound It is advisable to insert a Penrose drain, as well down into Morison's pouch and bring it out alongside the T tube The abdominal wound is then closed in the usual manner

SIDE-TO-SIDE ANASTOMOSIS OF COMMON DUCT AND DUODENUM

This method is particularly adaptable to strictures of the distal end of the common duct, as illustrated in Figure 14B It is preferable to actual transplantation of the common duct as described on page 110 particularly when there is any possibility that the stricture in the distal portion of the duct may reopen. The ampulla of Vater should always be preserved and utilized if at all possible because it is such an efficient mechanism and cannot be duplicated by the



Fig 19 Anastomosis of the common duct to the duodenum according to Sanders (91) using a longitudinal stoma in the common duct (17a) A Posterior row of interrupted silk or cotton sutures is placed, and a longitudinal opening is made in both structures. B An inside row of interrupted catgut sutures is placed. C The inside row is extended anteriorly and the outer row of interrupted sutures is completed

surgeon. This anastomosis may be performed by either (*1*) longitudinal stoma, or (*2*) transverse stoma, in the common duct.

Longitudinal Stoma in the Common Duct. If the opening in the common duct is made longitudinally as practiced by Sanders (91) and others the danger that the opening will be constricted by the reparative process is minimized (Fig. 19) The duodenum is mobilized by incising the peritoneum of the posterolateral portion and brought up so that it lies alongside the dilated portion of the common duct. A posterior row of interrupted silk or cotton sutures i then placed longitudinally approximating the common duct to the

duodenum. The common duct and duodenum are then incised (each longitudinally) and an inside row of catgut sutures applied There is less danger of constriction of the stoma if these catgut sutures are interrupted rather than continued however, if the opening is large enough a continuous suture may be used taking care not to pull it tight. After the inside catgut sutures are completed the anterior row of outside silk or cotton sutures is placed. The opening should be large enough to *admit the finger tip* Although food particles may escape from the duodenum into the common duct relatively few

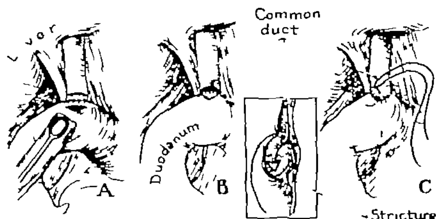


Fig. 20 Anastomosis of the common duct to the duodenum, utilizing a transverse stoma in the duct, A, Posterior (outside) row of interrupted silk sutures B, Inside row of interrupted catgut sutures. C Completion of outside row

cases of suppurative cholangitis will develop *when a considerable portion of common duct remains* In our opinion, entrance of food into the common duct is not an important causative factor of suppurative cholangitis when the opening into the duct is large and at least 3 or 4 cm. of the common duct remain.

Transverse Stoma in the Common Duct. In certain cases it may not be feasible to mobilize the duodenum sufficiently to allow longitudinal incision of the common duct, although the incision in the duodenum will obviously be longitudinal. As described in the preceding method an outer row of interrupted silk or cotton sutures is first applied representing the posterior layer (Fig 20) A transverse incision is then made in the common duct, and a longitudinal incision in the duodenum. An inner row of *interrupted* sutures of

fine catgut (3-0 or 4-0) is then placed After completion of the inner row of catgut sutures the anterior row of interrupted fine silk or cotton sutures is then applied as the outside layer

Either of these two methods is actually preferable to anastomosis between the gallbladder and duodenum, even in inoperable carcinoma of the pancreas if there appears to be sufficient tortuosity of the cystic duct to prevent free passage of bile If exposure cannot be obtained readily or there are widespread metastases so that death may be reasonably expected soon, the simpler procedure of cholecystoduodenostomy is advisable



Fig 21 Transplantation of the common duct into the duodenum (1 a) A Outer row of interrupted silk sutures B, Inside row of interrupted catgut sutures. C Completion of outside row

TRANSPLANTATION OF COMMON DUCT INTO DUODENUM

When the distal end of the common duct is completely destroyed the remaining portion of the common duct may be implanted into the intestinal tract For this procedure a technic must be chosen which will allow mucosa to-mucosa anastomosis of common duct and duodenum After opening or excising the end of the common duct so as to obtain as wide a lumen as possible a posterior row of interrupted silk or cotton sutures is placed between the common duct and the duodenum as shown in Figure 21 An inner row of interrupted sutures of fine catgut (3-0 or 4-0) is then applied to approximate mucosa to mucosa, after which the outside row of sutures is completed. If desired the inside layer of sutures may be placed first except that the posterior sutures of the outside layer are usually difficult to place if the inside row is completed first.

Such a procedure resembles those described in the preceding paragraphs. The results from this procedure are not satisfactory, particularly if the stump of common duct is short and of small diameter. Occasionally there is a tendency for the stoma to become plugged at intervals with food particles, but much more frequently it is apt

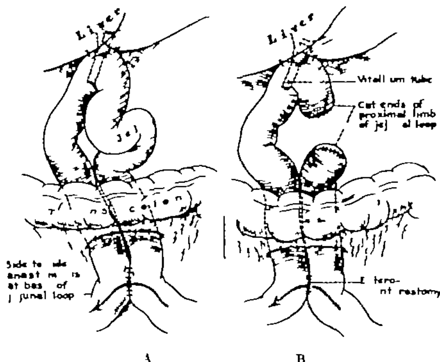


Fig. 22. Anastomosis of hilar duct to loop of jejunum. A. Entero-enterostomy with patency of the proximal arm resulted in failure (chills and fever) in 4 of the 5 cases so repaired. B. Severance of the proximal arm of jejunum resulted in complete cessation of chills, fever and jaundice in the 2 patients upon whom this interruption was performed. If a loop of jejunum is used, as illustrated in A, the authors recommend placement of folds in the proximal arm as shown in Figure 20.

to develop such marked stenosis that only a very small opening remains. We have used the procedure in only 1 case in this series and in this patient the stricture recurred in about a year.

ANASTOMOSIS OF HILAR DUCT TO LOOP OF JEJUNUM

The original operations undertaken by the authors utilized a loop of jejunum into which the hilar bile duct, with or without a vital

fine catgut (3-0 or 4-0) is then placed. After completion of the inner row of catgut sutures the anterior row of interrupted fine silk or cotton sutures is then applied as the outside layer

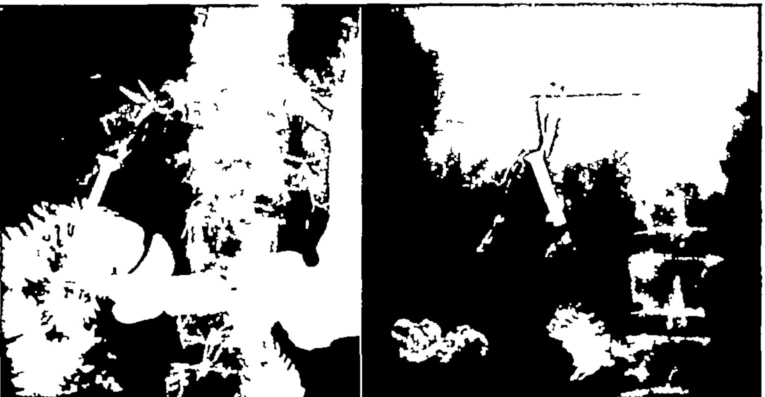
Either of these two methods is actually preferable to anastomosis between the gallbladder and duodenum even in inoperable carcinoma of the pancreas if there appears to be sufficient tortuosity of the cystic duct to prevent free passage of bile If exposure cannot be obtained readily or there are widespread metastases so that death may be reasonably expected soon the simpler procedure of cholecystoduodenostomy is advisable



Fig 21 Transplantation of the common duct into the duodenum (I a) A Outer row of interrupted silk sutures B Inside row of interrupted catgut sutures C Completion of outside row

TRANSPLANTATION OF COMMON DUCT INTO DUODENUM

When the distal end of the common duct is completely destroyed the remaining portion of the common duct may be implanted into the intestinal tract For this procedure a technic must be chosen which will allow mucosa to-mucosa anastomosis of common duct and duodenum. After opening or excising the end of the common duct so as to obtain as wide a lumen as possible a posterior row of interrupted silk or cotton sutures is placed between the common duct and the duodenum as shown in Figure 21 An inner row of interrupted sutures of fine catgut (3-0 or 4-0) is then applied to approximate mucosa to mucosa after which the outside row of sutures is completed If desired the inside layer of sutures may be placed first except that the posterior sutures of the outside layer are usually difficult to place if the inside row is completed first



A B

Fig 23. Roentgenograms following barium meal after anastomosis of the biliar duct to a loop of jejunum as shown in Figure 22A. Chills and fever developed in all 5 patients upon whom we performed this operation. In the two patients (A and B) whose roentgenograms are shown, reflux of barium was noted. The symptoms disappeared rapidly in both patients after the proximal loop was severed, as shown in Figure 22B although in one of the cases there was still a slight regurgitation of barium up the duct [illegible] of jejunum due to a [illegible] short loop.

lium tube splint, was implanted (Fig 22), and an enteroanastomosis performed between the two arms of the jejunum However, as indicated on page 112 results in this group (5 cases) were very poor One patient (no 24) died a few days after operation. The other 4 developed chills and fever (suppurative cholangitis) within a few weeks or months after operation. Roentgenographic study with a barium meal showed passage of barium past the enteroanastomosis up the proximal arm of jejunum into the intrahepatic bile duct in all 4 cases A second patient (no 23) developed liver abscesses and died several months after operation. In the third and fourth patients (nos 7a 8a) a second operation consisting only of sever



Fig. 24. Roentgenogram of the liver after a barium meal in a patient in whom the conventional anastomosis between duodenum and stump of common hepatic duct had been performed for a complete absence of the common duct (1"d) A rubber tube, which was passed a few weeks later was used in the anastomosis. Note the massive regurgitation of barium into the dilated intrahepatic ducts. The patient is having frequent chills and needs another type of repair but age and a cardiac lesion made him a poor operative risk.

ance of the proximal arm of jejunum was performed to prevent regurgitation The chills and fever promptly stopped and the patients have been asymptomatic ever since (3 and 4 years respectively) The fifth patient (no 22) refused a second operation after innumerable attacks of chills and fever she recovered and has remained asymptomatic to date (18 months) Although a few surgeons use this technic and appear to have fairly satisfactory results with it our results with the technic have been very poor We present evidence to prove that regurgitation of food and intestinal secretions into the liver can produce suppurative cholangitis even though no obstruction exists at the bile duct stoma.

ANASTOMOSIS OF HILAR DUCT TO ROUX Y ARM OF JEJUNUM

Before the decision is made to anastomose the bile duct to a Roux Y arm of jejunum, a thorough search must be made for the distal end of the common duct behind the duodenum and pancreas If it can be found an anastomosis between the two ends of the common duct with preservation of the sphincter of Oddi is decidedly to be preferred As has already been discussed (page 105) Cattell (13d) has described a new technic in which the duodenum and the pancreas are mobilized so that the head of the pancreas may be split and the distal end of the duct isolated The use of the Roux Y arm of jejunum in resection of the head of the pancreas for anastomosing the biliary tract to the intestine as popularized by Whipple (107a) has proved very applicable to the repair of strictures of the common duct The chief advantage of the Roux Y arm lies in the total elimination of regurgitation of food and intestinal secretion into the intrahepatic ducts Anastomosis of the open end of the biliary duct to the open end of the defunctionalized loop of jejunum also seems to be relatively free from the tendency to develop delayed stenosis which occurs so constantly when the end of the duct is implanted into the side of the bowel At first we thought it desirable to place folds or valves in the Roux Y arm of jejunum but we are now convinced that regurgitation will not take place even without folds provided the arm is at least 16 inches long.

The jejunum is severed about 15 inches distal to the ligament of Treitz The proximal end of jejunum is then anastomosed to the

distal jejunum at least 16 inches distal to the point of section. Either an end-to-side, or side-to-side anastomosis is used for this re-establishment of intestinal continuity We usually put in two rows of continuous catgut sutures for the entire line but if an end-to-side anastomosis is performed (Fig. 28 page 120), interrupted sutures using silk or cotton for the outside layer is preferable If a side-to-side anastomosis is utilized, the end of the proximal jejunum is of course turned in before the anastomosis is performed.

The defunctionalized arm of jejunum is then brought up to meet the hilar bile duct. If the mesentery of the jejunum is sufficiently long to allow the loop to reach around the colon an anticolic anastomosis is performed. If the mesentery is short an opening is made in the mesocolon and the jejunum is brought up behind the colon through this opening When a retrocolic procedure is used the edge of the mesocolon must be sutured to the arm of jejunum and its mesentery with numerous interrupted sutures to prevent herniation of this or another loop of intestine through the opening. With this procedure the bile enters the intestinal tract about 16 inches distal to the duodenum such an anatomic change with bile entering the intestine beyond the ligament of Treitz appears not to interfere with digestion

Several methods of attaching the end of the jejunum to the stump of the hilar duct are available If the stump of the hilar duct is long and large in diameter a two-layer mucosa to-mucosa suture line may be possible This is the ideal type of repair and will be followed by splendid results However since frequently no duct wall is available on most occasions a repair of this type is impossible, largely because the anastomosis must be made between the end of the intestine and the fibrous tissue at the hilus The recurrence rate in cases of this type is high as compared to the low rate when a stump of common duct is actually available This recurrent stenosis has interfered with obtaining an acceptable result, and has usually been associated with the return not only of chills fever and jaundice, but ultimately with liver abscesses and death *The tendency to recurrence of stenosis in patients without any duct at the hilus has become the greatest single obstacle to a successful outcome and attempts to prevent this stenosis have represented the major part of all recent surgical effort in this field*

We are convinced that some type of supporting structure in such a newly constructed stoma is desirable and usually necessary not only to prevent closure by edema immediately after operation, but primarily to support the opening during the healing process and thereby prevent stenosis Since cicatrization is not likely to cease for 10 or 12 weeks following trauma it would appear necessary to keep the supporting structure in place for at least that length of time

The internal splint should possess the following characteristics (1) It should provide adequate opening for bile flow (2) It should not collapse (3) It should remain in place long enough to keep the duct open not only during the period of complete healing of the mucosal anastomotic line but during the period of maximum connective tissue contraction. While we are not yet certain as to the exact length of time required for this degree of healing, a minimum of 3 months should probably be the aim. (4) It should be removable when it is no longer needed (5) It should not become occluded by bile precipitates

The two materials most commonly used as internal splints for the ducts are rubber and vitallium but neither is ideal. The advantages and disadvantages of these two procedures are discussed below

Vitallium Tube for Repair of Strictures

Introduction of the vitallium tube by Pearse (80a) opened the way for definitely improved results of operations designed to repair common duct strictures Nevertheless the problem of postoperative complications and recurrence of stricture has by no means been solved. The chief advantages of the vitallium tube are that vitallium is well tolerated by tissues and that the wall of the tube is comparatively thin thus providing a large lumen for the flow of bile. Its disadvantages are that it cannot be removed at a specified time it is rigid and it may become occluded with bile deposits

We have perhaps been more fortunate than many surgeons who have used these tubes since in only 2 of our cases have the tubes become obstructed In one of them (no 9) the tube dropped out of position into the Roux arm of the intestine and was therefore not functioning In the other one (no 23) the tube was in position and was distinctly obstructing bile flow We anchor the tube with only moderate security expecting it to pass in 3 to 6 months which may

support the stoma between the hilar duct and the duodenum the food stream, being pushed against the tube will invariably dislodge it probably at an early date and before satisfactory healing of the stoma takes place Moreover we are definitely of the opinion that any intestinal loop anastomosed to the hilar duct should be defunctionalized and not carry the food and intestinal secretions

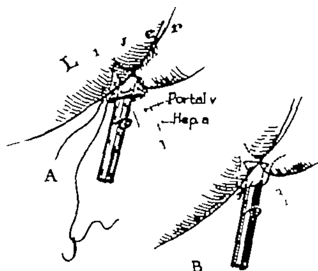


Fig. 26 Method of using vitallium tube (Pfd) A The stump of the duct is incised or dilated sufficiently to allow insertion of the funnel end of the vitallium tube A purse-string suture is applied preferably before the tube is inserted. B The suture is tied to achieve a watertight connection. If the bifurcation of the ducts is located close to the surface the tube shown may not allow free drainage in such cases a tube with a forked or Y-shaped end is preferable since both ducts can then be cannulated

Numerous types of vitallium tubes are available for reconstruction of the common duct (Fig. 25) Most are funnel-shaped at one end so that they may be anchored in place in the duct with a purse-string suture (preferably of silk) as illustrated in Figure 26 One type has a bifurcated end so that each hepatic duct may be connected if the common hepatic duct bifurcates before entering the liver In one of our patients (no 6) the hepatic ducts at the hilus of the liver were about ¾ inch apart and very inaccessible because of the enlarged liver The open ends of the ducts were so far apart

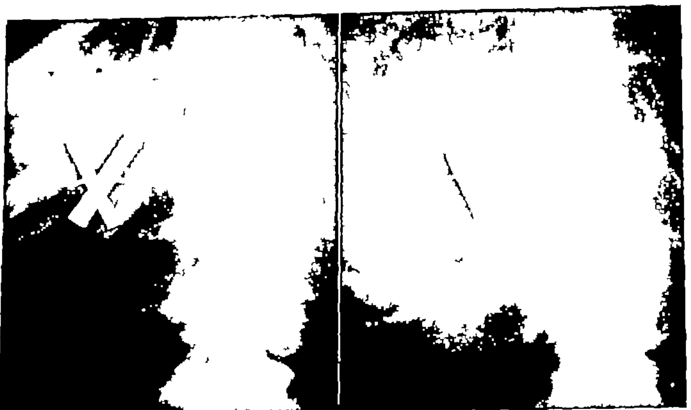


Fig. 27 Roentgenograms of case 6. In this patient the common duct bifurcated outside the liver the openings of the two ducts were so far apart that even a tube with a Y end (Fig 23) could not be used and a vitallium tube was inserted into each duct as shown at left The roentgenogram 6 weeks later at right shows that one tube was still in place

that a single vitallium tube with a bifurcated end could not be utilized We therefore used two straight vitallium tubes putting one in each duct (Fig 27) and brought the Roux Y arm of jejunum up to the hilus about both tubes Convalescence was excellent and in the first month after operation the patient gained 20 pound A roentgenogram 6 weeks postoperatively showed that 1 tube was still in place (Fig. 27) Except for an occasional chilly sensation the patient has remained free from symptoms in the 2 years since operation

The end of the jejunum can be attached to the bile duct in two or three ways The simplest is to invert the end of the intestine with a continuous catgut suture and insert the end of a Pean or Mixter

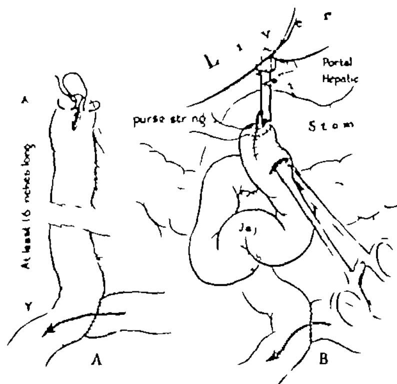


Fig 28. Method of attaching the end of jejunum to the bile duct (1 d) A After the ileum is severed and the proximal end is sutured to the distal loop at least 16 inches from the point of severance the distal end is closed with a continuous suture B The end of the vitallium tube is inserted into the end of the intestine aided by a hemostat passed through a puncture wound 2 or 3 inches from the closed end

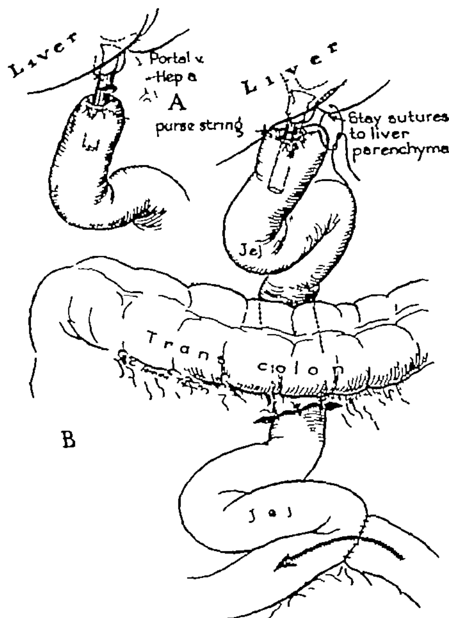


Fig. 29 Method of attaching the end of jejunum to the bile duct (17d) A, The connection between intestine and distal end of the vitallium tube is made tighter by applying a silk or cotton purse-string suture this is more easily applied before the tube is inserted. B, The end of intestine is anchored against the liver by interrupted sutures, all of which should be inserted before any one is tied.

forceps through the end of the intestine, as illustrated in Figures 28 and 29 so that the end of the vitallium tube may be guided with certainty into the lumen of the jejunum. The duct and the end of jejunum are anchored in place with 4 interrupted sutures previously placed but not tied until the end of the intestine is ready to be pushed up in place against the hilus of the liver

Another method of approximating the ends of jejunum and bile duct is to turn in the end of the jejunum, forming a cuff (1), which is then attached by interrupted sutures to the end of the bile duct. Theoretically this should tend to minimize stricture of the end of the intestine However, when the stump of duct at the hilus is extremely short the recurrence rate appears to be high, regardless of the method used In our experience when strictures at this point recur they do so primarily on the liver side. It would therefore appear that efforts to prevent recurrence must be directed toward the method of handling the end of the duct, and a method described on page 126 appears to us to offer a better opportunity for minimizing recurrences

When the wounds are closed omentum is brought up and sutured in place between the liver and intestine, to make dissection easier if another operation should be necessary A Penrose drain must be left in the upper portion of the wound, to allow for the leakage of bile which sometimes occurs depending on how securely the approximation between the ends of jejunum and bile duct has been made. However drainage of bile has not persisted for longer than 8 to 10 days in any of our patients

Rubber Catheter and Roux Y Arm of Jejunum for Repair of Strictures

In 1945 Allen (1) reported using the Roux Y arm of jejunum to re-establish the continuity between the gastrointestinal and biliary tracts He recommends insertion of a rubber catheter through the stoma to maintain patency of the lumen (Figs. 30–32)

Construction of the Roux Y arm is carried out as previously described. The end of the jejunum is turned in with numerous interrupted sutures forming a cuff 1.5 cm. long. An opening is made in the arm of the jejunum several centimeters from its end and the bell end of a catheter is threaded through the end of the jejunum. The end of the catheter is anchored in the hilar duct with a few interrupted absorbable sutures Several interrupted nonabsorbable sutures are placed between the end of the jejunum and hilar duct

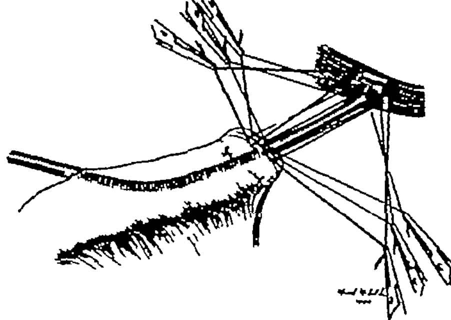


Fig. 30 Allen's method of using a catheter and Roux Y arm of jejunum (1a) Schematic representation of sutures of no 30 cotton thread placed through the scar tissue in the liver sulcus and through the jejunum. The bell end of the catheter has been fastened to the stump of the hepatic duct by two plain catgut sutures.

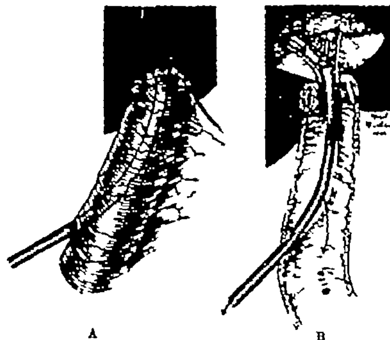


Fig. 31 Allen operation (1a) A, Appearance of jejunum after sutures to the liver have been tied. B, Schematic representation of the tube *in situ*.

(Fig. 30) and the sutures are tied after the jejunum is moved up against the hilus This maintains a watertight suture line. One or two holes are previously made in the catheter so that bile may drain

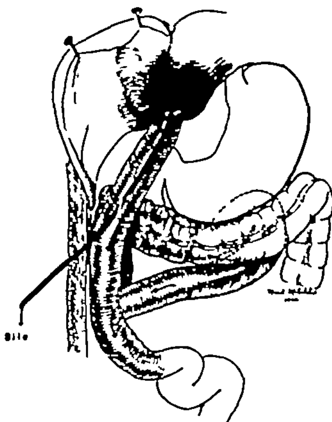


Fig. 32 Allen operation (Ia) Schematic representation of the completed operation. The proximal end of the jejunum has been reimplanted into the side of the distal end at a low level, and the tube in the hepatic duct has been brought out through an omental tab and a stab wound in the abdominal wall lateral to the incision.

either into the arm of jejunum or to the exterior (Fig. 31) The wound is closed bringing the catheter out through a stab wound in the abdominal wall lateral to the incision. A soft rubber drain, leading down to the anastomotic site is left in, to provide for possible leakage of bile. The catheter is left in place for 3 months,

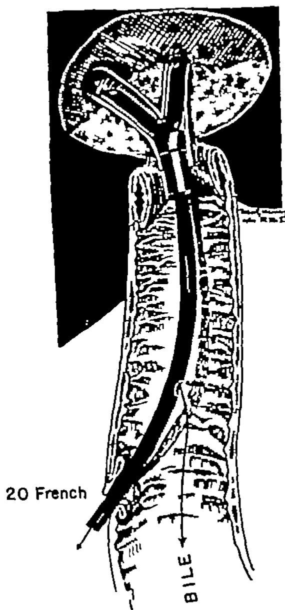


Fig. 33. Alternate method used by Allen. A vitallium Blakemore tube is placed over a Y-shaped rubber tube to assist maintenance of tube's position. (Courtesy of Arthur Allen.)

i.e., until cicatrization is practically over Recently, Allen (1b) has been threading a Blakemore vitallium tube over a Y rubber tube to facilitate holding the tube in place for the 3 month period (Fig. 33)

Mucosal Graft for Establishing Continuity between Hilar Duct and Roux Y Arm of Jejunum

In 1937 Hoag (42) reported a method based on the principle of formation of a cuff of gastric mucosa freed of muscularis for insertion into the opening of the bile duct at the hilus. This principle appears to us to have great merit, but unfortunately it has not received adequate attention. By Hoag's method, a small opening is made in the stomach, the mucosa is grasped and formed into a tube around a rubber tube 2 or 3 cm. long. The mucosa is anchored to the rubber tube with a few interrupted catgut sutures, the tube is inserted into the hilar duct opening, and anchored with a few interrupted sutures.

Because there is danger that gastric contents and food will be regurgitated with consequent inflammation, we have modified the procedure by forming a cuff of mucosa from the end of the Roux Y arm of jejunum. After constriction of the Roux Y arm, as described on page 114, we dissect the serosa and muscularis from the mucosa and submucosa with a sharp knife and scissors, for a distance of 2 or 3 cm. If the blood supply to the end of the jejunum has been preserved, the mucosal stump will likewise have sufficient blood supply to bleed at the cut edge. The entire cuff of mucosa is usually too large to insert with a rubber tube into the hilar opening, a wedge-shaped piece is therefore cut off (Fig. 34, p 146), and the cut edges reapproximated with very fine silk or cotton sutures. The mucosal cuff which results is anchored with 2 interrupted nonabsorbable sutures to a tube 2 or 3 cm. long (obtained by cutting off the bell end of a rubber catheter) The size of the catheter is determined by the size of the bile duct opening at the hilus. Two or three interrupted fine silk sutures are inserted from the outside of the hilar duct up into the lumen, about 1 cm. from the periphery back to the outside through the midportion of the tube and then through the wall of the hilar duct from the inside out. When the tube, with its surrounding cuff of mucosa is inserted into the hilar duct and the sutures are tied, the tube is held snugly in place making a watertight approximation. Two or three interrupted fine silk sutures can then be placed between the serosa of the jejunal stump and the liver tissue surrounding the duct. There is usually enough scar tissue in the liver in this area to hold sutures without danger of their tearing through.

As stated previously the least satisfactory results in the repair of strictures of the common duct are obtained in patients in whom no stump of common hepatic duct remains at the hilus. In our experience when strictures recur they usually are encountered at the margin of the liver, where scar tissue has actually replaced duct wall. On some occasions, a hole has had to be made at the hilus of the liver through dense scar tissue, through an area where the aspirating needle had withdrawn bile. Since the mucosal lining of the duct in this area has been replaced with scar tissue, it appeared to us that an epithelial graft might minimize cicatrization. We originally thought of using skin for this graft, but decided in favor of the mucosal graft, since, under the circumstances described, a blood supply would be preserved in the mucosal graft. This method has the obvious advantage of providing a tubular structure lined with mucous membrane which may be threaded so to speak, over a tube and into otherwise inaccessible areas. Presumably the technic just described should allow the scar tissue at the hilus of the liver to be bridged over, and intestinal mucosa to be brought to the mucosa of the intrahepatic bile duct. By anchoring the rubber tube in place with silk, it should remain *in situ* for several weeks, thus furnishing support during the healing process.

Analysis of Cases of Stricture of the Common Duct Encountered at Illinois Research Hospital

This analysis includes a study of 39 patients with strictures or absence of the common bile duct and upon whom we have performed 53 reparative operations during the past 9 years (Tables I–III).

TABLE I

Initial Cause of Benign Stricture of the Common Duct in 39 Patients Having 53 Operations

Cause of stricture*	Number of cases	Per cent
Operative trauma	25	64
Inflammation	8	20
Chronic pancreatitis	5	13
Pancreatic cyst	1	3
Total	*39*	*100*

* Only three patients, excluding the pancreatic group, were jaundiced before cholecystectomy

TABLE II. Thirty Nine Cases of Stricture of the Common Duct Arranged According to Operation Performed as Determined by Type of Stricture

Case no.	Age	Sex	Gallbladder removed, date	Interval between operation and jaundice	Repair date	Remarks	Results
			I. LESS THAN ONE-HALF INCH OF COMMON DUCT FOUND A. Hilar Duct to Roux Y Arm of Jejunum (Vitallium Tube)				
1	23	F	8/41	3 days	5/43	—	Excellent
2	35	F	12/41	Fistula 3 days later	1943 1946	Vitallium tube reimplanted 2d time results good	Failure in 1943 excellent in 1946
3	30	F	2/43	Few days	7/44	—	Excellent
4	36	F	1/43	3 days	5/43	—	Excellent
5	39	F	3/43	4 mos.	4/44	Died of Banti's disease 1 year postoperatively	Good (but see remarks)
6	31	F	6/40	3 days	7/46	2 tubes used duct bifurcated widely outside liver	Excellent
7 Same as 7A below	51	F	4/40	2 days	1/44	Converted to Roux Y by sectioning proximal arm of jejunum	Excellent
8 Same as 8A below	56	F	5/38	Jaundiced before cholecystectomy	10/43	Converted to Roux Y by sectioning proximal arm of jejunum	Excellent
9*	50	F	11/43	Fistula in few days	5/45 3/46	Stricture within liver	Failure, 1st operation excellent, 2d operation
10	64	M	6/44	Fistula in 2 days	4/45	—	Excellent
11 Same as 11A below	63	M	1/44	5 mos.	5/46	One attack of jaundice	Good

12	50	M	5/46	3 days	5/46	Stump of common duct necrotic at repair 5 days after cholecystectomy	Failure
13	30	F	5/45	Fistula in few days	5/46	—	Excellent
B. Hilar Duct to Mucosa of Roux Y Arm of Jejunum (Modified Hoag Operation)							
14 Same as 14A below	38	F	5/43	Fistula in 3 days jaundiced before cholecystectomy	11/46	Duct found in liver at depth of 1½ in.	Failure
15	28	F	3/46	Fistula in few days	10/46	—	Excellent
16	47	M	2/46	Jaundice 4 mos. later	12/46	Duct found in liver at depth of 1½ in.	Good
17	43	F	10/46	Fistula immediately jaundice later	2/47	—	Excellent
C. Hilar Duct to Roux Y Arm of Jejunum (Rubber Tube)							
18	48	F	11/41	Fistula in 3 mos.	12/42	1 hemorrhage esophageal varices	Good (but see remarks)
19	55	F	1/42	Fistula in 2 days	3/42	—	Excellent
20	44	F	3/45	Fistula in few days	9/45	—	Excellent
D Hilar Duct to Roux Y Arm of Jejunum (With Valves, No Tube)							
21	45	F	6/45	Fistula; jaundice in 2 days	9/45	—	Excellent

* Each patient had 2 operations of the same type the first was a failure, the second one was successful

Continued

TABLE II (*Continued*)

Case no.	Age	Sex	Gallbladder removed, date	Interval between operation and jaundice	Repair date	Remarks	Results (patency of duct)
E. Hilar Duct to Loop of Jejunum (Vitallium Tube)							
22	34	F	12/41	5 days	6/42	3 attacks of jaundice in 1945	Good
23 Same as 23A below	38	F	5/35	Few days	1943	Died liver abscesses	Died
7A	54	F	4/40	3 days	4/42	Proximal loop of jejunum cut later because of suppurative cholangitis	Failure
8A	56	F	5/38	Jaundiced before cholecystectomy	2/42	Proximal loop of jejunum cut later because of suppurative cholangitis	Failure
24	67	F	8/42	Fistula in 2 days	1/43	Died acute hepatic insufficiency	Died
F Hilar Duct to Duodenum							
25	53	F	1/38	4 years	7/45	Vitallium tube used in repair tube dropped out in few weeks	Excellent
26	52	M	2/38	Fistula in few days	4/39	Frequent attacks of chills and fever	Poor
27	50	F	7/33	3 days	12/37	Occasional mild chill	Good
23A	40	F	8/35	Few days	6/38	4 previous operations (hilar duct to duodenum) failed	Failure

II. NO COMMON DUCT Anomalous Duct to Pylorus							
28	40	F	9/37	Fistula in few days	6/39	Part of portal vein found missing at autopsy	Died
III PROXIMAL DUCT ABSENT A Hilar Duct to Common Duct (Vitallium Tube)							
29	32	F	1/43	5 mos.	10/43	Vitallium tube still in place bridging gap of 2 cm	Good
30	34	F	9/43	Fistula in few days jaundiced prior to cholecystectomy	10/43	Died liver abscesses	Died
IV DISTAL DUCT STENOSED BY CHRONIC PANCREATITIS A. Hilar Duct to Roux Y Arm of Jejunum							
31	48	M	Not removed	—	1944	No obstruction, but died 9/45 of unknown cause	Good

Continued

TABLE II (*Concluded*)

Case no.	Age	Sex	Gallbladder removed, date	Interval between operation and jaundice	Repair date	Remarks	Results (patency of duct)
			B Terminal Common Duct to Duodenum				
32	35	F	11/41	3 years	10/46	Choledochostomy 2/46 failed no obstruction after 2d operation, but pain of pancreatitis	Fair
33	37	M	4/43	Jaundiced 3 mos. prior to cholecystectomy	12/43	—	Excellent
			C Gallbladder to Loop of Jejunum (With Folds to Prevent Regurgitation)				
34	61	M	Not removed	—	9/46	Onset of jaundice 1/46 steatorrhea stool since 1943 operation 5/43 for suppurative cholangitis	Excellent
35	46	M	Not removed	—	1944	Multiple pancreatic stones abdominal pain	Excellent (but see remarks)
31A	45	M	Not removed	—	1943	Stoma closed in 6 months	Failure
			V OBSTRUCTION BY CYST OF COMMON DUCT IN PANCREAS Common Duct Cyst to Loop of Jejunum (With Fold to Prevent Regurgitation)				
36	36	F	Not removed	—	2/46	—	Excellent

VI OBSTRUCTION OF DISTAL END (CAUSE UNKNOWN)							
Transplantation of Common Duct into Duodenum							
11A	60	M	1/44	5 mos.	1045	For operation 5/46, see 11 above	Failure
VII LOCAL STRICTURES							
A. Common Duct to Common Duct (Vitallium Tube)							
14A	38	F	5/42	Fistula in 2 days jaundiced before cholecystectomy	11/42	Good results for 3½ years	Failure
B. *Mikulicz Repair*							
37	23	F	3/45	7 mos. after cholecystectomy	12/46	No jaundice at time of cholecystectomy	Excellent
38	32	F	5/40	No jaundice or fistula	11/46	Numerous attacks of pain in right upper quadrant since 1912	Died
C. *Removal of Adhesions*							
39	45	M	6/41	5 yrs.	5/46	Drainage of common duct for suppurative cholangitis, but only recovered after streptomycin administration	Excellent

TABLE III. Symptomatic Results and Operative Mortality Rate in 53 Operations on 30 Patients

Type of operation	Number of operations	Results	Operative deaths	Mortality rate, per cent
Hilar duct to Roux Y arm of jejunum				
Over vitallium tube	17 (on 13 patients)	10 excellent 3 good 4 failures	0	0
Over rubber tube	3	2 excellent 1 good	0	0
No tube	2	1 excellent 1 good	0	0
Hilar duct to mucosa of Roux Y arm of jejunum (modified Hoag operation)	4	2 excellent 1 good 1 failure	0	0
Hilar duct to loop of jejunum vitallium tube no fold to prevent regurgitation	5	1 good 4 failures (3 due to suppurative cholangitis; 1, to hepatic insufficiency)	1	20
Hilar duct to duodenum (mucosa-to-mucosa)	7 (on 4 patients)	1 excellent 2 fair 4 failures	0	0
Anomalous duct to pylorus	1	1 operative death	1	100
Hilar duct to common duct (over vitallium tube)	2	1 good 1 operative death	1	50
Dilatation and insertion of rubber tube through sphincter of Oddi past stricture in terminal end of common duct	1	1 failure	0	0
Terminal end of common duct to duodenum	2	1 excellent 1 good	0	0
Repair of local structures (1 by separating adhesions)	4	3 excellent 1 operative death	1	25
Transplanting common duct into duodenum	1	1 failure	0	0
Gallbladder to defunctionalized loop of jejunum	3	2 excellent 1 failure (stoma closed)	0	0
Common duct cyst to defunctionalized loop of jejunum	1	1 excellent	0	0
Total	*53*		*4*	*7.5*

Of the 39 patients 28 were women. Only 3 of the entire group (excluding those with obstruction due to pancreatitis) were jaundiced before their cholecystectomy, and had a choledochostomy, thus indicating what a small factor is drainage of the common duct alone in the etiology of stricture.

A number of operative procedures including the Roux Y arm of jejunum alone or supplemented by the Hoag modification, loop enterostomy, and choledochoduodenostomy, with or without rubber or vitallium tubes have been utilized in these operations.

Type of Stricture

The least favorable type of stricture for operative correction and permanent cure is that of complete absence of the common duct. This situation was encountered in 26 patients, upon whom we performed 32 operations in some of these patients a stump of less than 0.5 cm. was found at the hilus. This group will be referred to as type D (Fig. 14) The strictures of common bile duct which are readily correctable (type A) are those in which there is only a short defect. In our experience, this type is quite uncommon in only 4 of the 39 cases were the proximal and distal segments found patent and usable (Fig. 14) The remaining 9 cases were of types B and C, these include various miscellaneous defects of the common bile duct caused by stenosis distally or proximally, as a result of adhesions or chronic pancreatitis. In 1 case, a cyst was found at the terminal end of the common bile duct.

The strictures in at least two-thirds of the series were a direct result of operative trauma (Table I) In 5 patients (13 per cent) the stricture was definitely due to a diffuse, long-standing, sclerosing pancreatitis. With the exception of the 1 case due to a cyst, all others were classified as due to an inflammatory cause. We are of the opinion that in this group comprising 20 per cent of the cases, at least half were due to mild trauma which required time for a complete stricture to develop, the other half we assume to have been caused by abscesses or local collections of bile overlying the common duct. The lesions in the latter group might readily be classified as obliterative cholangitis We have ample proof of the pathologic process termed "progressive obliterative cholangitis", on several occasions we have found a fibrous cord as the only remnant

of a common duct which had been of normal caliber and perhaps used in an anastomosis at a previous operation.

It is interesting to note that the 25 cases due to operative trauma actually represent the type of stricture most difficult to repair At the time of the reparative operation, all of the patients with type D strictures had massive adhesions surrounding the porta hepatis In most of them, we were unable to find any remnants of common duct other than fibrous bands. Thrombosis of the portal vein, with portal hypertension and splenomegaly, was a complicating factor in 2 cases

Procedures Used

Roux Y Procedure This procedure has been used as a primary or secondary operation in 28 patients. We use it in all patients in whom the distal and central portion of the common duct are absent. In 17 of the above operations a vitallium tube was used in a few cases, short rubber tubes and in a few no tubes at all were used to support the lumen at the anastomotic line. We feel that a tubular support of some kind is indicated in practically all cases (page 115) Of the 22 primary operations of the Roux Y type (Table III) the results were classified as excellent in 13 (60 per cent) good in 5 (22 per cent) and as failures in 4 (18 per cent) In general these results are as good or better than in any other group

Hilar Stump to Loop of Jejunum. Reference has already been made to the very poor results that were obtained in the group of 5 patients, treated early in our experience in whom the hilar stump of the common duct was anastomosed to a loop of jejunum. In 2 of these patients with suppurative cholangitis, severance of the proximal arm of jejunum, without anything being done to the stoma resulted in complete cessation of symptoms

Mucosal Graft between Hilar Duct and Roux Y Arm of Jejunum. A modification of the Hoag procedure (Fig. 34) was used in 4 cases. The results in 2 patients (case nos 16 17) have been excellent. In the other two, one may reasonably assume that no type of operation would have been successful the duct could not be found at the hilus and an opening $1^1/_2$ inches long had to be made through liver tissue to a duct which we located with the help of the aspirating needle about

1½ inches to the right of the hilus. One of these patients made a satisfactory convalescence for several months, but has since died, the other is getting along fairly well with no chills, but an icterus index of 20 However, sufficient time has not elapsed for the recur rence which we expect may develop

Anastomosis of Hilar Duct to Duodenum We performed 7 con ventional operations, consisting of anastomosis of the hilar duct to the duodenum by the mucosa to-mucosa technic The result can be considered entirely successful in only 1 case (no 25), 2 are classified as fair results, the remaining 4 were failures. The results of this procedure in our hands have been too poor to justify its routine use.

End to-End Anastomosis. A Mikulicz type of plastic repair was performed on 2 patients with local stricture. The result was excel lent in 1 case (no. 37), the other (no. 38) died postoperatively

There were 2 other cases of local stricture in our series. In one (no. 14A) anastomosis of the two ends was performed over a vitallium tube the patient remained entirely well for 3 years at the end of which time there was a recurrence of jaundice. Roentgenographic examination showed the tube to be missing presum ably it had passed down the duct, through the sphincter of Oddi, and into the intestine. At the second operation we found no trace of the common duct the ends of which had been found at the previous operation and anastomosed together We could not find the duct at the hilus, but anastomosed the end of a Roux Y arm of jejunum to a hole 1½ inches deep into the liver at a point where with an aspirating needle we found a bile duct which we opened. The patient died a few months later

The fourth patient (no 39) with a local stricture came into the hospital with chills and fever of 2 weeks duration, indicative of suppurative cholangitis and probably small liver abscesses A local stricture was corrected by dissecting it out of a bed of adhesions, and the duct was drained with a T tube. Choledochostomy and peni cillin were ineffectual in relieving the fever which was finally con trolled with streptomycin. Culture of the bile was positive for Escherichia coli, streptococci and staphylococci. The patient has been symptom-free to date.

Other Types of Repair In 5 patients the stricture was located in the terminal end of the common duct, the cause being a chronic sclerosing pancreatitis (Table II cases 31–35) In 3 of these the *gallbladder was anastomosed to a loop of jejunum, folds* or valves being placed in the ascending limb of the jejunum and a jejunojejunostomy performed to prevent regurgitation. Roentgenograms showed the procedure to have been effective Results were excellent in 2 patients (nos 34,35), in the third (no 31A), the stoma closed, and another operation utilizing the Roux Y arm of jejunum was performed with good functional results (no. 31) This patient died 1 ½ years later of unknown cause. In another patient (no. 33), with stricture due to pancreatitis an anastomosis was performed between the side of the common duct and the duodenum with excellent *results In the fifth patient (no. 22) a choledochostomy was* performed with dilatation and insertion of a rubber tube up into the pancreatic portion of the common duct. This patient remained sympton free while the tube was in place (3 months), but after the tube was passed symptoms again recurred. At another operation an anastomosis was performed between the common duct and duodenum results are classified as good the duct remaining patent, but there are complaints of pain, apparently caused by the pancreatitis.

In one patient (no 36) a cyst of the terminal end of the common duct located in the head of the pancreas was producing pain and partial obstruction. The cyst was pointing anteriorly and had flattened the head of the pancreas to such an extent that we were able to split the pancreas and anastomose the cyst to a loop of jejunum in which we placed 2 folds in the ascending arm and performed a jejunojejunostomy This procedure completely relieved the pain

In patient no 11 with a stricture of the distal end of the common *duct of unknown etiology we transplanted the duct* into the duodenum. The duct was considerably dilated and we therefore thought that the lumen at the anastomotic line was large enough to remain open permanently However the stricture recurred within a year Another operation was performed consisting of an anastomosis between the stump of the common duct and the end of a Roux Y arm of jejunum over a vitallium tube Except for one or two mild chills *there has been no evidence of obstruction of the duct since* this operation.

Use of Vitallium Tubes Almost all the vitallium tubes which we have implanted have ultimately passed, although 2 or 3 have remained in situ 2 or more years. When they remain in place longer than 6 months, there is a distinct danger of their becoming occluded by bile precipitates Some surgeons have noted obstruction frequently, but it occurred in only 2 of our cases In one, the tube had become dislodged from its position at the stoma into the Roux Y arm of the jejunum, it may or may not have been occluded at the time it slipped out of position. In our opinion, the tube need not stay in place for longer than 4 months However in strictures at the hilus where the mucosa of the duct has been replaced by scar tissue, there will be a high incidence of stricture formation, even though the supporting tube remains in place longer We are hoping that the mucosal graft which we are using in such patients (modified Hoag operation) will minimize the cicatrization.

Altogether we have made use of a vitallium tube in 22 cases, in 4 instances they have had to be replaced because they had become obstructed or had slipped out, and the stricture had reformed. Not all of these tubes were used in Roux Y operations We used a vitallium tube in the 5 early cases in whom we anastomosed the hilar duct to a loop of jejunum. As stated previously we have abandoned this procedure because it permits regurgitation of food and secretion into the liver, but the tubes were in no way responsible for the 4 failures in this group A vitallium tube was also used in 1 patient with a local stricture (no. 14A), and in 1 patient with the proximal portion of the duct missing (no. 29) In the former, the tube passed and the stricture recurred at the end of 3 years. In the latter the tube was still in place when the patient was last seen 3 years after operation, but there were no signs or symptoms of biliary obstruction. A vitallium tube was used in another patient (no. 25) to support the suture line of an anastomosis between duct and duodenum the tube passed in a few weeks. Although the result in this patient was very good, we believe that a vitallium tube should not be used in this type of operation, since the end of the tube protrudes into the lumen of the duodenum and the food stream obviously must dislodge the tube in a very short time.

In cases of this type it is our practice to insert a rubber tube which is long enough to bend into the lumen of the duodenum, and the tubes have remained in place for as long as 3 months This is

an ideal length of time as far as support of the anastomotic line is concerned

In 1 patient (no. 6) we were forced to use 2 vitallium tubes the common hepatic duct bifurcated outside the liver The stricture had occluded both the right and left hepatic ducts so that separate drainage had to be provided to both ducts. The two branches entered the liver at points so widely apart that the two arms of the tubes already available with a Y bifurcation at one end would not reach the ducts. The end of the Roux Y arm of the jejunum was brought up and anastomosed to the hilus of the liver over the two tubes (Fig. 27) A roentgenogram taken 6 months after operation revealed only 1 tube in place (Fig. 27) The patient had 2 or 3 mild attacks of chills and fever but during the last few weeks has been asymptomatic

Operative Mortality

In the 53 operations there were 4 operative deaths a mortality rate of 7 6 per cent. The first (no 24) was a 67 year old woman who had suffered from a persistent external biliary fistula, with chills and fever ever since a cholecystectomy had been performed (elsewhere) 5 months previously A defect in the proximal portion of the common duct was repaired by anastomosing a loop of jejunum to the hilar duct over a vitallium tube. The patient's marked liver insufficiency was increased still further by a postoperative wound infection. Recovery was also retarded by a deep femoral thrombosis prior to the reparative operation. The albumin globulin ratio was reversed. This patient died 3 weeks postoperatively of hepatorenal failure with a markedly elevated blood nonprotein nitrogen The signs of hepatic insufficiency came on very insidiously with a gradually progressive lowering of blood pressure and temperature to subnormal This was accompanied by apathy inanition, and a marked decrease in urinary output despite liberal supplementary therapy with parenteral fluids blood plasma, glucose oxygen and adrenocortical extract. Although we recognized that she was a very poor operative risk improvement under intensive preoperative care was so poor that further delay appeared unjustified

The second (no 28) was a 40 year old woman. In 1937 this

patient was diagnosed as suffering from acute empyema of the gallbladder, for which a cholecystostomy was performed. Cholecystectomy was done 1 year later at another hospital, 10 months after the gallbladder was removed jaundice chills and fever developed and became progressive, 5 months later the patient developed an external biliary fistula, which persisted until she entered the Research and Educational Hospital, 8 months after its onset, for the reparative operation. In addition to the jaundice chills and fever, the patient also suffered from severe secondary anemia nutritional edema, mitral stenosis and marked hepatic insufficiency as determined by liver function tests. At operation, there was a complete defect in the common bile duct and in the portal vein and as a result of the latter there were tremendously dilated portal varices. A hepaticoduodenostomy was performed over a no 18 rubber catheter with considerable difficulty because of the dilated veins and dense adhesions. Death occurred 2 weeks postoperatively due to diffuse bleeding from all the mucous membranes apparently a result of the severe liver insufficiency The marked decrease in prothrombin (3 per cent of normal) was irreversible despite administration of vitamin K and whole blood.

The third (no 30) was a 34 year old woman, jaundiced prior to cholecystectomy in September 1943 who developed an external biliary fistula within a few days after operation. In this instance, a reparative operation was performed 1 month after the cholecystectomy and an excellent result was expected but signs of sepsis developed, and the patient died 5 weeks later At operation, the hepatic duct was found to bifurcate before entering the liver and lacking a Y tube a single tube was introduced into one of the ducts. At autopsy it was found that this tube had partly slipped out of the duct in which it had been placed and blocked the other (right) duct. A large abscess was found in the right lobe of the liver

The fourth (no 38) was a 32 year old woman, who had had a Mikulicz type of repair for a local stricture. Death occurred about 2 weeks after operation. Autopsy did not disclose definitely the cause of death, but it may have been in part occasioned by the profuse regurgitation of duodenal contents into the liver through the arm of the T tube this had been threaded out through the sphincter of Oddi because a stenosis had also been found at this point.

Indications for the Various Operations in Common Duct Strictures

Local Stricture

As intimated previously, the simplest type of stricture to repair is one that is localized and involves no more than a few millimeters of the duct. Occasionally Mikulicz's operation, consisting of a longitudinal incision and transverse repair may be used. However to maintain patency a T tube must be inserted at a point proximal or distal to the stricture, and the arm carried up past the anastomotic line *The tube must be left in place for at least 3 months to* prevent cicatricial contracture.

Usually, however so much of the duct wall is involved that a plastic repair of the Mikulicz type is impossible, in such cases the stricture should be resected and an end to-end anastomosis performed Mobilization of the duodenum will allow sufficient upward shift of the distal end of the duct to achieve repair without tension. As in the method described above, a T tube must be inserted through an opening either proximal or distal to the suture line so that the arm of the tube extends beyond the row of sutures.

Stricture or Absence of Distal Portion of Common Duct

When the stricture is limited to the distal end of the common duct, two or three types of repair are available for correction of the obstruction. The simplest method is probably to anastomose the dilated duct to the duodenum which may be done by means of a longitudinal or transverse incision in the common duct (Figs. 19,20) The *longitudinal incision (Fig. 19) offers a distinct advantage over the* transverse because a larger opening can be made with the former It is agreed, however that an unusually long opening cannot insure against constrictions since the size of the stoma cannot actually be any *larger than the diameter of the common duct.* While a third method is available, namely, transplantation of the duct into the duodenum (Fig. 21) the authors prefer one of the above-mentioned procedures if at all possible. Under ordinary circumstances any one of these three methods of anastomosing the common duct to the duodenum will be associated with regurgitation of food and intes

tinal secretion from the lumen of the duodenum up into the common duct. However, neither of two patients in whom we performed a side-to-side anastomosis between a long stump of common duct and the duodenum developed chills. This favorable result is in contrast to a high incidence of recurrence of chills and fever in 7 patients in whom the duodenum was anastomosed to a very short stump of duct at the hilus. As suggested previously, it is our belief that the common duct acts as a reservoir for regurgitated material thus protecting the liver. Therefore if a stump of common duct is still present, the need for using a defunctionalized loop of intestine in the repair is less urgent.

When the stricture is only partial, there is no need for a radical operation of the type just mentioned. The first obligation of the surgeon is of course, to explore the common duct thoroughly with scoops and probes for stones, which may or may not be found in addition to a real stricture. If it is difficult to get a large probe through the lower end of the duct and the sphincter of Oddi a supporting tube should be inserted and left in place for 2 or 3 months. A T tube with a long arm may suffice for the purpose, but frequently it will be impossible to get the tube through the distal duct and sphincter of Oddi without opening the duodenum for assistance in guiding the tube. However we are not certain that this procedure of inserting a long armed T tube is without danger since the operative death of case 38 occurred in a patient in whom we had inserted one arm of a T tube up toward the liver past an area where a local stricture had been repaired by the Mikulicz procedure and the other arm downward through the sphincter of Oddi because of a stenosis in the distal portion of the duct. On the other hand we have never seen any untoward results from the insertion of a short tube (4 to 6 cm.) into the distal duct from the opened duodenum in addition to insertion of a T tube with short arms in the midportion of the common duct. If a tube large enough to fit snugly in the duct at the sphincter of Oddi is chosen it will remain in position for 6 to 12 weeks. When the gallbladder is still present and not badly diseased, it may be utilized in the anastomosis, provided the cystic duct is patent and bile is found in the gallbladder. For reasons discussed below the authors do not consider that the indications for this type of operation* are very strong unless there is a possibility that the stricture is temporary as

* That is, cholecystojejunostomy

when caused by pancreatitis When performed we emphatically advise the use of a defunctionalized loop of jejunum with folds or valves in the proximal arm to prevent regurgitation. Even with this precaution, the incidence of closure of the cholecystojejunostomy stoma after 2 or 3 years is extremely high (probably over 50 per cent. Closure of the stoma in obstruction due to carcinoma (usually of the pancreas) will rarely be encountered, even following the classic operation of cholecystoduodenostomy because the patient almost invariably succumbs before this length of time has elapsed. We wish to emphasize again, as has been stressed by Cattell (13d), that the surgeon must search extensively on the posterior surface of the duodenum and head of the pancreas for the distal stump of the common duct before deciding upon a procedure which prevents use of the sphincter of Oddi

Stricture of the Proximal End of the Common Duct

When the stricture involves the upper end of the common duct (Fig. 14) an attempt should be made to mobilize the duodenum sufficiently to bring the distal end of the duct up to meet the proximal end. Since the sphincter of Oddi is such an important structure this is the operation that should be used if at all possible If the distal end of the common duct can be found it will almost always be possible to mobilize the pancreas and duodenum sufficiently to bring the two ends together and perform an end to-end anastomosis over an arm of a T tube inserted into the duct distal to the suture line If it is impossible to make the two ends of the duct meet a different type of procedure must be adopted. Of the methods available in such a case anastomosis of the end of a Roux Y arm of jejunum to the hilar duct will probably be the most satisfactory

Stricture or Absence of the Entire Common Duct

As indicated previously most of the strictures encountered in our series were of the type in which no common duct whatever could be found. This does not mean that all of the common duct had been excised. On two or three occasions, we have performed a repair in which we utilized segments of common duct, but at a later operation found them to be entirely obliterated Opening the duodenum to search for the sphincter of Oddi we have not found to be very

helpful. In patients with a patent duct the sphincter can be found, but when the duct is truly stenosed and has been in disuse for several weeks or months we have practically never been able to locate the sphincter of Oddi and catheterize it with a probe from the duodenal side

When a short stump (½ to 1 cm.) of the proximal duct remains at the hilus an actual mucosa to-mucosa suture between the duct and the end of the defunctionalized Roux Y arm is possible, and should be the operation of choice. In such cases good results are to be expected. However, when no remnant of duct can be found at the hilus the recurrence rate will be high, for it is then impossible to carry out a true mucosa to-mucosa procedure In our opinion, a modified Hoag operation, as illustrated in Figure 34 offers the best chance of cure in such a patient, with fibrosis at the hilus of the liver Theoretically the cuff of mucosa will act as a graft and thereby minimize the stenosing process. We have not had sufficient experience with this operation to prove the point but in our limited experience with 4 patients we have been very favorably impressed with its possibilities Animal experiments are being carried on to determine how readily this cuff of mucosa adheres to the scarred liver tissue.

The two other mechanisms available for anastomosing the stump of the duct to a defunctionalized loop are (*1*) anastomosis over a vitallium tube or (2) anastomosis over a catheter (1a) In the authors opinion, these two procedures should yield about the same results. Theoretically the procedure of forming a cuff at the end of the jejunum and anastomosing it to the stump of the common duct as recommended by Allen should minimize the stenosing factor However in our experience, the primary site of the stenosis is located on the bile duct side of the anastomosis In any event, a supporting tubular structure of some type should be kept in place for at least 3 months.

Congenital Atresia of the Bile Ducts

Obstructions of this type are perhaps the most unfavorable for operative repair of all encountered fortunately they are comparatively rare In a study of 45 cases Ladd and Gross (56) found that only 20 per cent were operable, i e., with any evidence of extra hepatic duct or gallbladder connecting with the intrahepatic ducts

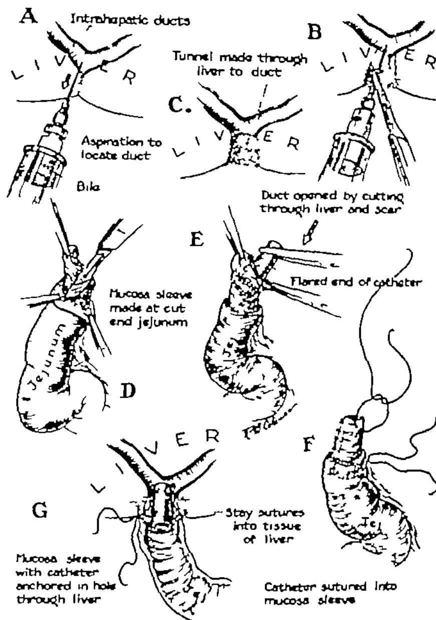


Fig. 34 Modification of Hoag procedure now being used by the authors when no duct protrudes at the hilus of the liver (17b) A, Locating the duct by aspiration. B, Entering the duct by following needle with knife. C, Tunnel made through the liver to duct. D Separating the serosa and muscularis from the mucosa and submucosa. E, Excising a portion of the mucosa (at the dotted line) to make the mucosal flap fit a rubber tube (bell end of catheter) F Anchoring the tube to the flap which is closed with interrupted, fine silk sutures. G Inserting the flap, together with the tube up into the opening in the hilus and anchoring it by a few interrupted silk sutures.

(Fig. 35) In our experience, the percentage of operable cases is even smaller

Signs and Symptoms The diagnosis of congenital atresia of the bile ducts can rarely be established definitely before the age of 5 or 6 weeks. The mild jaundice which these infants show up to this age is usually interpreted by parents and physicians alike as being due to icterus neonatorum. The persistent, complete absence of bile from the intestinal tract is the basis upon which the diagnosis is finally established. The liver is large and firm, but smooth to palpation, and

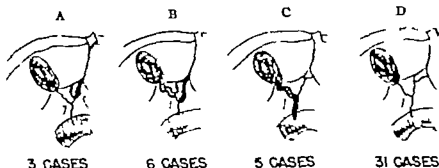


Fig. 35 Types of congenital atresia of the extrahepatic bile ducts, as found in surgical exploration of 45 cases (56) A, Hepatic duct patent and connecting with the liver B Hepatic duct and part of common duct patent gallbladder atretic or patent. C, Hepatic duct atretic gallbladder and cystic and common ducts normal. D Hepatic and common ducts atretic.

the spleen is also enlarged. Bile-stained ascitic fluid is commonly present in the peritoneal cavity, particularly in infants who are several months old. The child's appetite is usually unimpaired, at least for a few months and nutrition surprisingly good. The stools are, of course, acholic Suppurative cholangitis is extremely rare

Treatment. Although these babies may live for 12 to 18 months with complete obstruction of the common bile duct, operation should be advised as soon after birth as the diagnosis can be made with certainty (Fig. 36) If a dilated end of common duct can be found, it should be anastomosed to the intestine. The authors agree with Ladd and Gross (56) that this anastomosis can be performed between the duct and duodenum and that the probability is very slight that ascending infection from the duodenum will develop Moreover the inaccessibility of the duct makes anastomosis with a defunctionalized loop of jejunum more difficult than the above procedure. When the gallbladder contains bile, and there is apparently a satis-

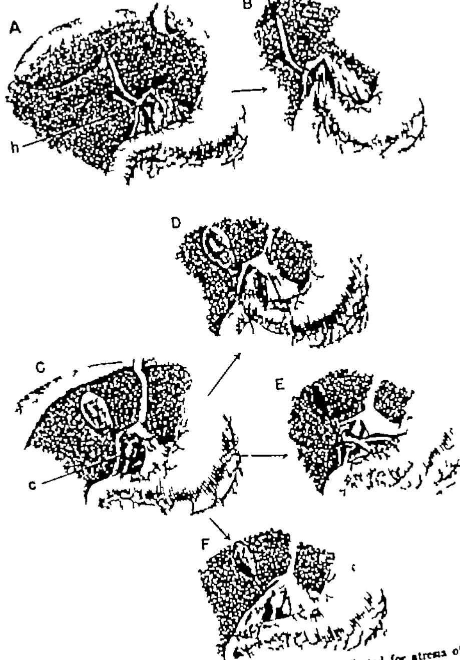


Fig. 36. Types of operative relief which have been effected for atresia of bile ducts (56). A, Atresia of hepatic duct treated by hepaticoduodenostomy as shown in B. C, Atresia of the common duct treated by choledochoduodenostomy, cholecystogastrostomy and cholecystoduodenostomy as shown in D, E and F respectively. Choledochoduodenostomy is believed to be a better procedure than the two latter procedures mentioned. h, Blind end of hepatic duct. c, Blind end of common duct.

factory opening through the cystic duct into the hepatic duct, the gallbladder may be anastomosed to the stomach. However, Gross (38) has found it necessary to convert a cholecystogastrostomy into a cholecystenterostomy because the bile entering the stomach seemed to be a factor precipitating severe digestive disturbances

When no gallbladder or duct containing bile can be found the entire liver including particularly the region of the hilus should be aspirated with a syringe and hypodermic needle in the hope of finding a dilated duct. We have even resorted to amputation of the left lobe of the liver hoping to find a dilated duct which could be anastomosed to the intestinal tract, but without success In congenital atresia, the extreme fibrosis and regenerating liver cells seem to compress the ducts and prevent their dilatation.

We have not included our cases of congenital atresia of the common duct in the series reported here, primarily because the technic of repair is so different from that in adults

Congenital Cystic Dilation of the Common Duct

Obstruction of this type is rare and seldom diagnosed except at the operating table. When there is only a single cyst, as is usually the case, treatment is comparatively simple and consists of anastomosis of the dilated area to the intestine, preferably the jejunum. Such cysts are usually found in the common duct superior to the duodenum but in one case recently encountered by the authors details of which are being reported elsewhere, the cyst had developed in the pancreatic portion of the common duct. The cyst had presented through the head of the pancreas which had so flattened out that an anastomosis could be made between the loop of the jejunum and the anterior portion of the cyst, exposed by an opening made through the inferior portion of the pancreas If the cyst is large, we recommend an enteroenterostomy and folds in the ascending loop (Fig. 39) to prevent food from accumulating in the cyst.

Preoperative and Postoperative Care of Patients with Stricture of the Bile Duct

Preoperative Care

Patients with stricture of the bile duct may occasionally be in fairly good physical condition and ready for surgery when first seen

by the surgeon. More often however, *they require special attention* in preparation for operation.

The problems which these patients present are usually four in number namely sepsis jaundice, malnutrition and fluid imbalance.

Sepsis As indicated previously the sepsis results primarily from stenosis but as discussed on page 112, regurgitation of food and intestinal content may occasionally be the causative factor Obviously, no treatment short of providing a free flow of bile or elimination of regurgitation will relieve this complication. Chemotherapy should of course be tried When obstruction is not corrected by operative drainage the authors have seen no benefit from penicillin therapy in these patients, but two or three times streptomycin favorably affected the sepsis. This response may perhaps be explained by the fact that Escherichia coli is supposedly the most common and most virulent organism involved although streptococci and staphylococci may also be present. In general adequate surgical drainage must be established in these cases A culture of the bile should invariably be taken following drainage and the appropriate chemotherapeutic or antibiotic agent administered The systemic improvement to be expected from chemotherapy high caloric diet, transfusions, and other measures, lessens the operative risk.

Jaundice and Cholepremia Oral administration of bile in those patients in whom bile can be collected is often of greater benefit than oral administration of desiccated bile or bile salts. One of our patients gained 15 pounds in 12 days when given a high caloric diet and his own liquid bile by mouth. Surprisingly many patients with a total biliary fistula find bile not only tolerable but actually palatable. When patients cannot tolerate bile by mouth it may be given once a day through an esophageal catheter With much less discomfort, but with probably less effect, the bile obtained from a T tube or fistula may be injected into the rectum. This procedure should be adopted rather than discard the bile. If no biliary fistula exists thus preventing use of the procedures just mentioned bile should be given by mouth in the form of desiccated whole bile. Vitamin K, also, should be administered parenterally, although it is not to be considered as a substitute for bile.

Malnutrition. One patient lost 60 pounds (a drop in weight from 140 to 80 pounds) during the 4 months in which she suffered from a total external biliary fistula, a fact difficult to explain in this case.

Administration of bile by mouth was possible for only a short time, the patient being unwilling to undergo the prolonged period of observation which would have been necessary to restore a reasonable amount of weight. Vitamin K administration did not improve the nutritional status. But in the first month after the hilar duct was anastomosed to the intestine the patient gained nearly 30 pounds, an indication of how important bile is to the general nutrition.

Anemia and hypoproteinemia must be corrected by blood transfusions and administration of plasma and amino acid solutions, as well as by careful attention to diet.

Fluid and Electrolyte Imbalance We have seen patients with choledochostomies who have lost such large quantities of bile as to precipitate a hypochloremic state (46) This, obviously, is less apt to develop while a stricture without fistula is present, since no bile is lost to the exterior, but when bile is being lost through an external fistula, careful attention to the quantity and type of electrolyte lost is necessary in order to prevent serious deficiency

In addition to the use of blood in the preoperative preparation of patients, patients must also be given blood during the operation. Even though the loss is no more than that encountered during the average laparotomy blood should be given at a rate of about 500 cc. per hour of operating time.

Postoperative Care

In general, most of the therapeutic procedures of preoperative care must also be utilized during the first few postoperative days and longer if complications develop For the first day or two the most important precautions are maintenance of adequate fluid balance and blood transfusions. Chemotherapeutic agents specifically aimed at the organism found in the bile must be administered. Special and constant attention must be given to restoring and maintaining the normal prothrombin level by administration of vitamin K.

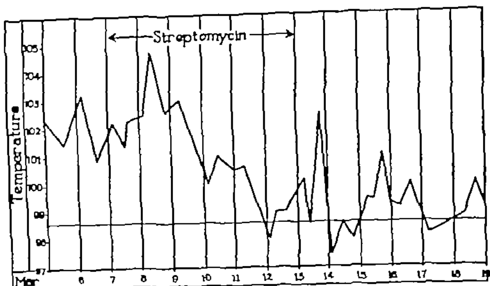
Local accumulation of bile must be avoided if at all possible. For this reason the Penrose drains which are placed in the abdomen about the site of the anastomosis and hilus of the liver must be left in place for several days, in case a biliary fistula should develop If they are taken out too soon, the skin and abdominal wall may close before an eventual leak at the site of anastomosis occurs.

Although the immediate postoperative course is often surprisingly good, occasionally the sepsis, which forms one of the greatest hazards presents formidable dangers One patient, who was too ill to support anything more than a choledochostomy at the first operation developed a liver abscess postoperatively On draining the abscess not only pus but bile was obtained During the very prolonged convalescence huge pieces of necrotic liver emerged through the incision used for draining the liver abscess After this necrotic material had been evacuated bile drained freely and the patient improved so markedly that in a few weeks the operation could be completed and the bile duct anastomosed to the intestine (Roux Y arm of jejunum) The patient is now almost entirely free from symptoms

Complications of Common Duct Strictures

Cholangitis due to Esch coli staphylococci, or streptococci is a common complication in stricture of the common duct, and if free drainage is not established promptly will progress to the formation of liver abscesses (Fig 37) These pyogenic abscesses are usually multiple and frequently fatal (Fig. 38) For this reason, delaying operative repair of a stricture is undesirable On the other hand the adhesions developing in the right upper abdominal quadrant as a sequel of a biliary fistula are dense and extremely vascular for several weeks after the development of the fistula making operation very difficult, and one is tempted therefore to postpone the reparative operation for a few weeks. But delay is unwise if chills and fever are present.

After repair of the stricture many patients will have an occasional chill without increase in jaundice if treated conservatively these temporary reactions will as a rule disappear They may be caused by plugs of mucus which lodge in the stoma and obstruct it or if a defunctionalized loop of intestine is not used food particles might perhaps block the stoma. Chemotherapy may be employed during these attacks sulfadiazine 4 Gm. per day along with copious amounts of water may be of definite prophylactic value in preventing a prolonged infection. Sulfasuxidine or sulfathalidine 12 and 6 Gm per day respectively may be given although we have not noted any pronounced benefit from these drugs Whether or not bile salts should be given during these temporary attacks is still a matter of controversy If an obstruction is present a cholagogue might theo-



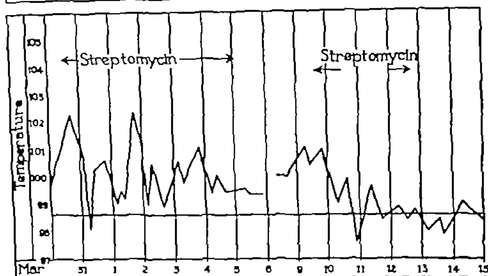


Fig 37 Chart of a patient who had had a choledochostomy to relieve chills, fever and jaundice produced by a stricture (caused by massive adhesions) 8 days before streptomycin therapy was begun on March 8 (17c) Drainage of the common duct had not relieved the fever and other signs of sepsis, indicating that small liver abscesses were probably present. Blood culture at time of operation yielded Escherichia coli, and culture of bile from the common duct also showed the presence of the same bacillus. Constant administration of penicillin had brought no improvement. The first course of streptomycin caused a slight drop in the fever after the third course, the fever subsided and the patient remained well. In our opinion, streptomycin saved this patient's life after penicillin and choledochostomy had failed.

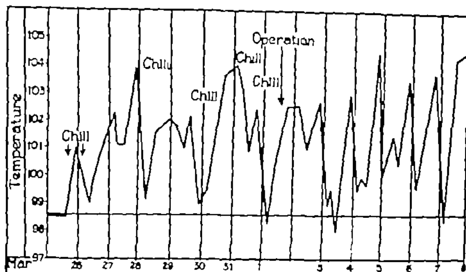


Fig 38. Chart of a patient in whom drainage of the common duct (no obstruction found) was ineffective in controlling fever because of the presence of multiple small liver abscesses, as proved 3 weeks later by autopsy (17c) Note the frequent chills. Penicillin was given throughout the period illustrated, and was likewise ineffective. Culture of the bile showed Esch. coli and Staphylococcus albus.

retically be harmful yet such therapy would tend to make the bile less viscid and therefore probably minimize the deposits of mucus and bile precipitates.

Results

It is difficult to assay results of operative repair of common duct strictures because the great variety of strictures encountered require several different types of operations and recurrences may develop years after repair The authors are of the opinion that if the two ends of the duct can be approximated end to-end anastomosis over a T tube or vitallium tube will yield the best results good to excellent results should be obtained in over 80 per cent of cases. Cattell (13d) is likewise of the opinion that this method should be superior to others, and accordingly splits the pancreas in an effort to find the distal end He reports the u e of vitallium tubes in 23 patients with end to-end anastomosis 2 of the patients died postoperatively and satisfactory results were obtained in 19 or 90 per cent of the re-

maining 21 cases In the 2 remaining cases the tubes became obstructed and had to be removed. Our results with the vitallium tube in end to-end anastomosis have not been so successful, but the series is too small for conclusions to be drawn. In our opinion, the T tube in end to-end anastomosis has the advantage of being removable at a specified time.

As stated previously, we obtained good to excellent results in 82 per cent of 22 cases utilizing the Montprofit Roux Y arm of jeju num, a vitallium tube was used to support the anastomotic line in 17 of the cases. Utilizing the Montprofit-Roux Y arm of jejunum and a catheter draining outside, as well as into the lumen of the tube, Allen reports good results in the 8 patients in whom this procedure was used although 3 of them had transient attacks of chills, fever, and jaundice.

Pearse (80e) has summarized the results as given in numerous reports on the use of vitallium tubes. In the 106 cases which he col lected in which a vitallium tube was used to support the anastomotic line in end to-end suture of the duct, good results were obtained in 80.1 per cent, and in 11.3 failure was caused by occlusion of the tube. In 79 cases, a vitallium tube was used to anastomose the hilar duct to the duodenum with good results obtained in only 58.2 per cent. We agree with the conclusion Pearse draws, namely, that vitallium tubes should not be used when the duct is anastomosed with the duodenum.

In our hands, anastomosis of the hilar duct to the duodenum or any other functioning loop of intestine has given very poor results. In a small series of 7 cases with hepaticoduodenostomy there was complete failure in 4, in the remaining 3 cases, results were only fairly good in 2. In 25 cases surviving hepaticogastrointestinal anastomosis reported by Cattell (13), 12 or 49 per cent are listed as being well and 4 additional cases or 16 per cent as being improved, though all 4 patients had occasional attacks of jaundice or fever If the in testine is to be anastomosed to the hilar duct, Cattell prefers to use a loop of jejunum, performing an enteroanastomosis between the two loops. We have been able to demonstrate a reflux of barium into the intrahepatic bile ducts in practically all patients with this type of repair who are given barium provided the patient is turned from side to side and observation extends over an hour or two. Accord ingly we now always make folds or valves in the proximal arm when

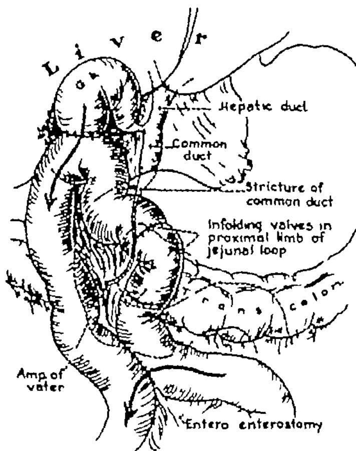


Fig. 39 Anastomosis of gallbladder to loop of jejunum which has been defunctionalized by placing 2 or 3 folds or valves in the proximal arm to prevent regurgitation of food into the gallbladder (80f) This type of anastomosis is not very satisfactory for permanent strictures of the common duct, since stenosis is so apt to occur at the stoma. For the temporary stricture produced by localized pancreatitis, however or for carcinoma of the pancreas it is entirely satisfactory With the latter lesion the patient is apt to die before stenosis develops.

we anastomose a duct or any other structure to a loop of jejunum (Fig. 39) although we much prefer to utilize a Montprofit Roux Y arm. On the other hand Walters (103b) prefers choledochoduodenostomy or hepaticoduodenostomy to other procedures he reports that in a consecutive series of 40 patients who had undergone either of the two procedures 69 per cent were living and well when last

heard from (8 patients for more than 5 years and 8 other patients for 3 to 5 years) "

The mortality rate will naturally vary depending upon the nutritional status of the patient and the degree of infection or hepatic insufficiency Our mortality rate was 7.5 per cent in 53 operations. Cattell (13) reports a mortality rate of 13.8 per cent in 123 cases and Walters a mortality of 10 per cent in 98 cases. Numerous transfusions, great care in combating nutritional imbalance, and intensive treatment of infection in the biliary tract by chemotherapy are absolutely essential. However, now and then, patients will be encountered in whom hepatic damage is so great or nutritional imbalance so serious, that achievement of even moderate operative risk is impossible.

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Factors Influencing the Regeneration of Nerves

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Nature of Nervous Regeneration

The recovery of function by an interrupted nerve is one of the clearest examples of the body's tendency to maintain its integrity in spite of injury However anyone who has dealt with cases of nerve injury and has watched the painful slowness of recovery after nerve suture and seen the imperfection of the final result, may be forgiven for finding this particular provision of Nature tantalizing or even positively ironical. Another time seeing the complete recovery which follows a simple compression of a nerve one realizes that the power of regeneration is very strong, and is led to wonder whether it might not be possible to find some means of obtaining equally good recoveries in other types of nerve injury such as are unfortunately so common in time of war

A very great deal of attention has been devoted to the matter by research workers and clinicians but so far no really spectacular improvements of technic have emerged Nerve regeneration still depends essentially on bringing the severed ends together and allowing new fibers to grow from the cut surface to the end organ we have no means of accelerating this relatively slow process. However the knowledge which has been gained shows us which factors are most likely to retard the recovery and produce an imperfect final result. The modern surgeon is thus provided with more and surer guides than his predecessors had to help him in making a prognosis and in deciding whether when, and how to operate This knowledge together with a better understanding of how important is the care of patients with denervated limbs and atrophic muscles has made possible recoveries after nerve injury which are distinctly better than those formerly attained.

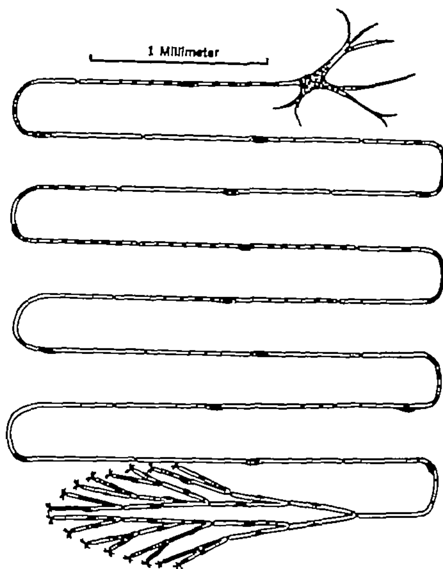


Fig. 1. Diagram of a short somatic motor nerve cell and its fiber drawn strictly in proportion to show the immense elongation. The fiber is 20 μ in diameter and 2 cm long. In longer and thinner fibers, the length may be a million times the diameter

peculiar physical properties of living matter It is not unlikely that such a system will show rapid changes from liquid to solid states Besides the protein molecules which make up this colloidal solution

the axoplasm of course also contains many substances in true solution. There is much potassium but little sodium or chloride within the nerve fiber and this difference maintained across the invisible axilemma membrane covering the fiber, is probably responsible for the difference of electric potential between the inside and outside Breakdown of the membrane by natural or artificial stimulation causes discharge of this potential through neighboring parts of the fiber which discharge in their turn and so propagate an action potential

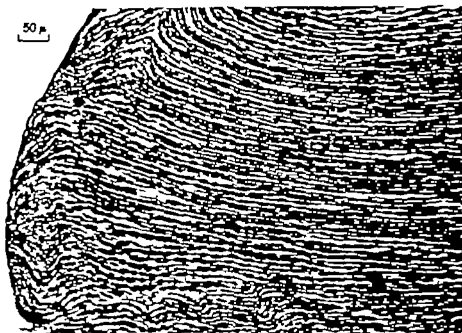


Fig. 2 End of piece of normal rabbit peroneal nerve fixed and stained with the Bodian method. The fibers show an unduloid outline

Probably all nerve fibers have at their surface a thin layer of phosphatide molecules and this is thickened on the larger fibers of mammals to make the myelin sheath. The function of this is to increase the conduction velocity though it is not yet completely clear how the effect is achieved The myelin is interrupted at intervals by the nodes of Ranvier which are spaced farther apart in the larger than in the smaller fibers it has been suggested they play an important part in conduction the impulse leaping from node to node.

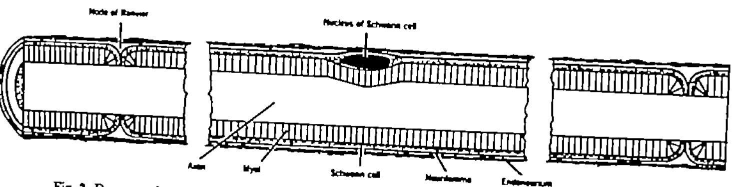


Fig. 2. Diagram of normal, medullated nerve fiber The axon should be shown narrower at the nodes.

However it was recently shown (33a,77,87) that after regeneration of a nerve the internodes are of the same short length on all fibers whatever their diameter Yet Sanders and Whitteridge (55) showed that the larger fibers of regenerated nerve conduct faster than the smaller in fact at the same speed as normal large fibers in spite of their short internodes It is doubtful therefore, whether the nodes play an essential part in conduction. Probably the longer internodes of the larger fibers result from the fact that those fibers medulla e earlier so that the internodes are more stretched by growth after they have been laid down.

A possible function of the nodes is to prevent the movement of the myelin under mechanical stress Separate elongated drops of this sort would be much less easily displaced in a tube than would a continuous column. However nodes occur so far as is known on all medullated nerve fibers (contrary to common opinion they are present in the central nervous system) and their function remains uncertain.

The myelin is produced by the interaction of the axon surface with the protoplasm of a special satellite cell the cell of Schwann, often called a neurilemma cell (Fig. 3) A single Schwann cell nucleus lies near the center of each internode the protoplasm extends over the whole surface as a network of strands but is so thin as to be seldom visible in a cross section of a fiber except near the nucleus

All the components so far described are soft and protoplasmic they are fully enclosed in a tube of more rigid material whose inner wall is the neurilemma—a thin, smooth membrane composed of very fine fibers mostly running in a circular direction. It lies immediately outside the Schwann cell and was regarded by Schwann himself as the outer membrane of that cell. Although its exact composition is uncertain, it is evidently of a scleroprotein nature, and is not a cell membrane in the sense of a layer at a protoplasmic surface controlling diffusion in and out of the cell. It covers the Schwann cell closely and turns in over the end of the myelin at the nodes continuing as a somewhat complex structure, the cementing disc which occupies the gap between the myelin segments

Outside the neurilemma the wall of the tube is further strengthened by coarser collagen fibers mainly longitudinal forming the sheath of Henle or sheath of Key and Retzius and con inued as the endoneurium by which the various fibers are bound together and

which contains *fibroblasts and vascular tissues* *It is very important for an understanding of nerve regeneration to appreciate that each nerve fiber is surrounded by a definite tube* These tubes remain when the axon and myelin have degenerated and serve to guide regenerating fibers back to the denervated tissues

Around each bundle of nerve fibers there are several lamellae of a peculiar connective tissue the perineurium Denny Brown (11) has shown that *the cells of these lamellae are a peculiar flattened form of fibroblast and the sheets are smooth and resemble mesothelium. The various bundles* making up a nerve are bound together by a further membrane the epineurium to form a single trunk.

A peripheral nerve thus contains a considerable quantity of supporting and protecting connective tissue far more than is present around the bundles which form the white matter of the central nervous system *This is the reason for the very marked difference* in the consistency of the two tissues The white matter is so soft as to *be almost liquid whereas a peripheral nerve forms a strand suf* ficiently tough to be mistaken at times for a tendon! Peripheral nerve fibers can certainly stand a great deal more rough treatment than central ones which is no doubt one of the reasons why physiologists have discovered so little about conduction in the long pathways of the central nervous system

Types of Nerve Injury

The events which may interrupt conduction in a nerve may be classified as—chemical thermal ischemic and mechanical

Chemical Damage to Nerve The interruption of a nerve by chemical means is chiefly of importance not as an accident but when used intentionally *as by injection for the relief of pain* Alcohol is generally used for this purpose though convenient and immediately effective in interrupting nerves it does not prevent regeneration and in experimental *animals other substances (gentian violet formal* dehyde) have been found more effective (27) Accidental injection of sulfonamides into nerve *is another example of chemical interrup*tion (36) it leaves the tissue in a very unfavorable state for regeneration and is therefore a most serious mishap Another important type of chemical effect on nerve is that produced by toxic neuritis either from lead or other poisoning or the toxins of diphtheria or other living agents We may also include in this category

interruption by the neurotropic viruses, especially that of poliomyelitis For completeness, the effect of deficiencies such as of thiamin producing beriberi or of copper producing sway back in lambs may also be classified as examples of chemical interruption of nerve

Thermal Damage to Nerve This has been of interest chiefly from the effects of cold in cases of "immersion foot" and similar conditions (76) The situation is then always complicated by vascular changes but it is possible that in severe cases chilling interrupts conduction directly by upsetting the metabolism of the axoplasm or by the formation of ice crystals Application of very low temperatures directly to nerve, as by contact with frozen carbon dioxide can produce interruption in this way

Ischemic Damage to Nerve Lewis and Pochin (45) made a careful study of the effects of various durations of ischemia on human nerves. Loss of conduction was usually only temporary but in two cases where a cuff was applied to a finger a paralysis was produced from which recovery began after 10 weeks This therefore, presumably involved Wallerian degeneration, and the lesion may be compared to that of an axonotmesis as described below In cases where the blood supply is permanently diminished as by the formation of scar tissue around a nerve the conduction may be interrupted without Wallerian degeneration. In such cases freeing of the nerve by the operation known as "neurolysis has been held to produce a dramatic and rapid recovery but the value of this procedure is still doubtful and there has still been too little study of such conditions for us to be able to discuss them further In general there is at present a tendency to regard ischemic lesions of nerves as being more common and serious than was formerly supposed (35,51 62) Injection of substances containing colloidal particles may produce damage to a nerve through thrombosis and ischemia from endarteritis may be a cause of serious effects

Mechanical Damage to Nerve It is obviously not easy to separate effects of mechanical conditions on the blood supply of nerve from traumatic interruption of the axons We may therefore approach the problem by inquiring how much compression nerves can stand and what is their reaction to various forms of injury Denny Brown and Brenner (12) made a careful investigation of the effect of compression of nerves by various forces acting for various times using simple spring clips attached to the sciatic nerve of cats They found that after a clip corresponding to a weight of 170 to 430 Gm

had been applied for 2 hours signs of impairment of conduction in the motor fibers appeared and persisted after removal of the clip. Sensory fibers were not affected, since the cats still responded to pin prick applied to the toes. The motor paralysis *continued only for a* short time, movements becoming fully normal again after about 2 weeks. There had evidently been no Wallerian degeneration of the fibers and histologic examination showed that the axons were intact but that there was local destruction of the myelin at the nodes in the region which had been compressed.

They also compressed nerves continuously with weaker clips and found that up to 7 Gm. there was no interruption of conduction although changes appeared in the myelin. Clips of 9 to 10 Gm. produced delayed paralysis after 5 to 9 days with recovery after 23 days. Clips of 44 Gm., continuously *applied produced Wallerian* degeneration. Denny-Brown and Brenner considered that all the effects observed were due to ischemia and some of them could be produced by compression of the whole limb with a tourniquet.

These most important experiments show that it is possible to produce a nerve lesion which blocks conduction without causing death of the portion of the fiber peripheral to the lesion. It is not clear exactly why conduction over the damaged region is impaired; the recovery *did not always clearly coincide with the laying down* of fresh myelin. Clinical experience has long recognized that transient paralysis of this sort may occur and Seddon (60) has recently suggested the term "neurapraxia" for the condition. The characteristic feature is that although conduction through the nerve may be *wholly lost it returns within one month, that is to say, before re-*generation by outgrowth of new axons could possibly take place. During the period of paralysis sensation is little if at all affected. Faradic excitability is retained in the region of nerve peripheral to the lesion and the muscle fibers of the territory affected do not *waste or fibrillate. Beyond this little is known of the condition or* the changes in nerve and muscle which accompany it. Presumably it should be possible to recognize various degrees of damage, with increasingly long times necessary for recovery.

Degeneration of Nerve Fibers after Axonotmesis

More severe compression of a nerve interrupts the axons and myelin completely, producing Wallerian degeneration. The connective tissues of the nerve *may be left intact, however, producing*

what the surgeon recognizes as a "lesion in continuity" Seddon suggests that this condition may be called axonotmesis and, on acquaintance, the term will be found to be convenient and less difficult to use than might be expected at first.

A simple means of producing this lesion experimentally is to compress a nerve with a pair of forceps having smooth blades. Study of sections of nerves fixed at various times after such an operation has shown that the axons are interrupted but that the supporting tubes are left as channels along which regenerating fibers can advance to regain their old connections. Crushing a nerve in this way therefore provides a valuable means of producing a standard nerve lesion from which recovery is rapid and complete. The pressure must be strong if it is to interrupt all the fibers but if the blades of the forceps are ridged or the pressure is applied in such a way as to disrupt the endoneurium, then fibers will fail to regain their old channels and regeneration will not be complete.

It is not known exactly how pressure applied to the nerve acts to cut off continuity with the nerve cell body The axoplasm is certainly squeezed aside by the pressure it may be found as large masses distending the tubes above and below the lesion (Fig. 4) Strands of darkly staining material can be seen at the level of the compression itself and these persist for some days thereafter They are the "preserved fibers" which Cajal (9) noticed after various types of lesion. Probably therefore severe pressure coagulates the axoplasm forming a thread of denatured protein between the central and peripheral stumps.

When such a barrier is interposed it is clear that there is no possibility whatever of any rapid primary union of the severed portions of the axons. It is an interesting question whether such reunion could occur if conditions were suitable. The observations of Speidel (70) and of Levi (43) suggest that it is a possibility Working, respectively with fibers in the tail of the tadpole and with nerves in tissue culture they have shown that the stumps of a single severed axon may reunite. In both cases the matter is complicated by the fact that, on account of the plexiform arrangements of the nerves studied the fibers on *both* sides of the cut were sometimes though not always connected with cell bodies These observations at least show that two strands of axoplasm may, under suitable conditions, come together and unite This is further suggested by the conditions over the surface of a severed central stump as described below



Fig 4 Rabbit peroneal nerve fixed with Bodian method 10 minutes after crushing with smooth-tipped forceps The axons have been interrupted and masses of axoplasm are seen on both sides of the lesion the framework of the nerve is intact

Even though such unions may possibly occur it is important to recognize that there is no clinical or experimental evidence that primary union of this sort plays any part in the recovery of nerve lesions in mammalian nerves If the lesion effectively detaches the peripheral from the central stump the isolated portion rapidly undergoes Wallerian degeneration and can only be replaced by the

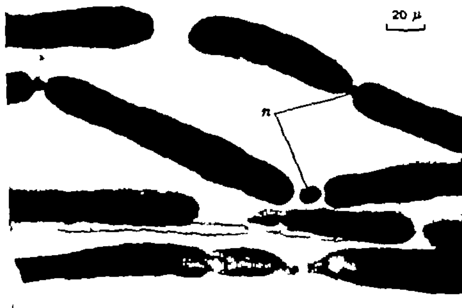


Fig. 5 Portion of distal stump of rabbit nerve severed 4 days previously The fibers are breaking up into long ovoids between which neck droplets (n) are seen. Osmium tetroxide teased preparation.

slow process of outgrowth from the central stump It is not yet certain why degeneration proceeds in the isolated section or to put it conversely what is the influence which the cell body and nucleus normally exercise over the peripheral portions of the fiber The sequence of events during degeneration gives us some clues however In adult mammals fibers in the isolated trunk begin to drop out during the second day the larger fibers failing first (30) no fibers conduct after the ninetieth hour The histology of the stages of degeneration which precede the breakup of the fibers has not been adequately studied but from the fortieth hour onward interruptions begin to appear They take the form of constrictions which narrow



Fig. 4 Rabbit peroneal nerve fixed with Bodian's method 10 minutes after crushing with smooth-tipped forceps The axons have been interrupted and masses of axoplasm are seen on both sides of the lesion the framework of the nerve is intact.

the myelin to a neck and finally break it, often leaving one or more small droplets between the separated ends These constrictions occur at intervals along the fibers, which thus become divided into a series of long, sausage-shaped sections (Fig 5) Each section then breaks again into shorter portions until the fiber is reduced to a series of spheres or ovoids two or three times as long as they are broad (see Fig. 6)

This process suggests most forcibly the division of a long cylinder of liquid under surface tension We have seen evidence already that both axon and myelin can behave as liquids and as such they might be expected to tend to break up in just this way, a long liquid



Fig 7 Fibers of rabbit peroneal nerve teased in Ringer's solution and examined in polarized light. Note unduloid outlines with meiosural cracks (i) in the troughs of the waves n, node of Ranvier

cylinder not being a stable figure. There is indeed ample evidence of this tendency Axons show unduloid outlines under a variety of conditions for instance near the end of any piece of nerve which is simply cut out of the body and placed in fixative (Fig. 2) Similarly the myelin of fibers teased out in Ringer's solution is usually unduloid (Fig. 7) The appearances seen during degeneration recall the operation of surface forces most vigorously (Figs. 5 and 6), even the details of the formation of neck and secondary neck droplets are similar to those shown by physicists to occur during the breakup of liquid columns under surface tension.

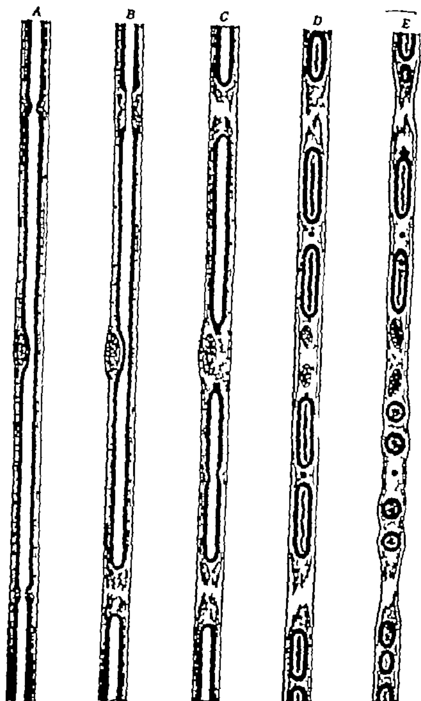


Fig. 6 Diagram showing the stages in the breakup of myelin and axon and the increase in Schwann cell protoplasm during nerve degeneration. In *C* and *D* the myelin becomes unduloid and breaks, forming ovoids and primary and secondary neck droplets. The Schwann cell protoplasm increases continuously and the nucleus divides.

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Figs. 12 and 13 Fibers central to point of rabbit nerve cut 5 days previously The axons (ax) have divided into numerous strands, which in Figure 12 (at left) reunite lower down. Bodian stain.

large or small and in a later communication Hammond and Hinsey (29) recognise this.

Of the very large number of fibers which thus grows down the tubes only a fraction survives a relatively short time after a crush lesion the peripheral stump has approximately the normal number of fibers, distributed in the case of a muscle nerve, in the normal bimodal manner (24) (Fig 15) One of the most interesting results of recent work has been to show that this reduction in number only

occurs if the new fibers make contact with the periphery. Weiss and Taylor (83) noticed that if the fibers of a nerve are made to regenerate into two channels that channel which allows them to reach the periphery will come to contain the larger fibers. Sanders and Young (57,58) used the method of crushing nerves of the rabbit high up in the thigh and cutting them low down. On one side the stumps



Fig. 14. Portion of peripheral stump of rabbit nerve crushed with smooth-tipped forceps 15 days previously. Very numerous small nerve fibers are seen running as bundles in the tubes. Bodian stain.

are joined at the lower end, but on the other side of the animal this is prevented. Regenerating stretches of nerve are thus provided below the crushed points: the fibers can reach the periphery on one side of the animal, but on the other side they end in a neuroma (Fig. 16). Examination below the crushed point 100 or 200 days later showed that on the side where they ended in a neuroma both sensory and cutaneous nerves contained very numerous small fibers, whereas the nerves which were connected with periphery approached their normal composition.

There is therefore without doubt an influence exerted from the muscle or sensory end organ up the regenerating nerve. Presumably

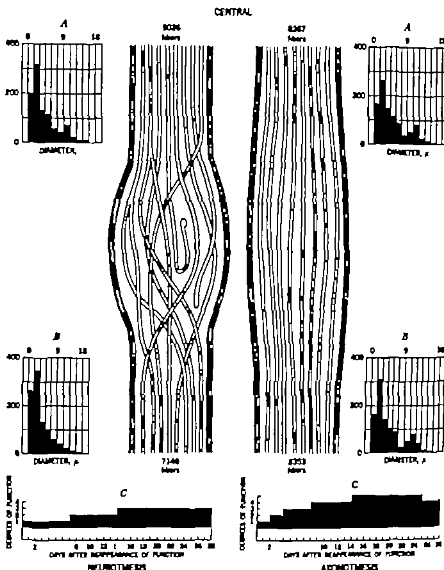


Fig. 15 Diagram showing contrasting results of nerve regeneration 300 days after severance and suture (neurotmesis) and crushing (axonotmesis) of the peroneal nerve of the rabbit The histograms of the condition of the central stump (*A*) show the shrinkage of fibers after neurotmesis. The histograms of the peripheral stumps (*B*) show that normal bimodal pattern is restored only after axonotmesis. The data for the numbers of fibers are those of Gutmann and Sanders (24) for the speed and degree of recovery of spreading of the toes after two operations (*C*) data are taken from Gutmann (10) Normal action is shown as degree 4 which is never reached after neurotmesis, whereas after axonotmesis there is a phase of excessive activity

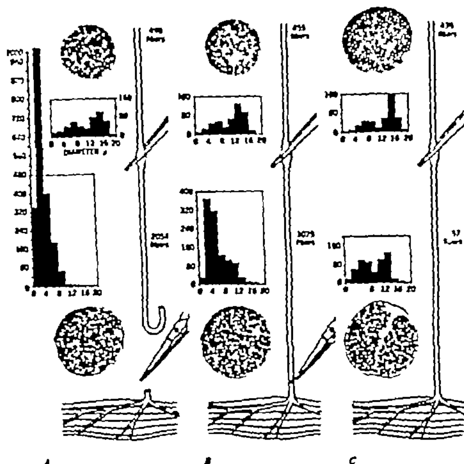


FIG. 16 Effect of peripheral connection on regeneration All 3 nerves are crushed with forceps above but are treated differently below *A* is cut and left without union *B* cut and sutured *C* untouched and all then left for 100 days At the top photos and histograms of the central stump show the shrinkage of fibers in *B* and especially in *A* Below are shown the conditions of the nerves 1 cm. below the crush there are very many small fibers in *A* a unimodal distribution of larger ones in *B* and an almost normal nerve in *C* From data of Aitken, Sharman, and Young (3)

when one of the many small new fibers makes contact with a suitable end organ this influence passes up it so that it begins to grow much more rapidly than its fellows *and actually causes them to disappear* More recently we have investigated the phenomenon in more detail using the nerve to the lateral head of the gastroenemius muscle in the rabbit which contains about 400 fibers (3) One hun

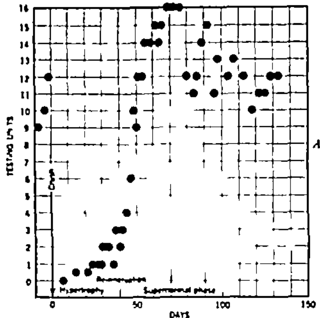
dred days after this nerve had been crushed and arranged so as to prevent the new fibers from reaching the periphery as many as 4 000 fibers were found below the crush (Fig. 16A) and their diameter was small. *After 150 or 200 days*, about the same number of fibers were present and they were no larger However when the nerves were arranged so as to allow union with the periphery the nerve below the crush contained only 1 000 fibers after 100 days and some of these were large (Fig 16) If the nerve was not interrupted below the crushed point, the number of regenerated fibers was still further reduced and the bimodal distribution of fiber sizes normally found in the muscle nerve was already restored after 100 days (Fig. 16C)

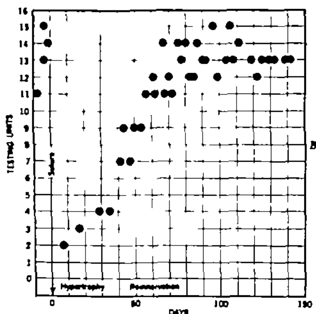
This very striking influence of the periphery thus acts relatively rapidly It was found that union with any muscle even one normally antagonistic could produce the effect. Important from a surgical *point of view is the fact that muscles moderately wasted by de-*nervation atrophy proved able to induce maturation of the nerve, but the power of the muscle to do so was considerably reduced by tenotomy Nerves which have been allowed to regenerate for some time without reaching the periphery can mature if *later allowed* to do so

It remains to be discovered how this remarkable ascending effect is produced by the muscle on the nerve Weiss *et al* (82) suggest that perhaps when a fiber makes contact with its end organ some alteration reduces the surface energy needed for the restless changes of an unattached nerve fiber Further work must answer this question and also show us whether the effect is produced by simple contact with the muscle or other end organ or whether as seems not impossible nerve tissues like other tissues, increase in amount with the use which is made of them by the body

RECOVERY OF FUNCTION AFTER NERVE COMPRESSION

A nerve which has been crushed may therefore regenerate a normal fiber pattern and correspondingly there can be a complete return of normal function. Clinicians have long been familiar with the satisfactory sensory and motor recovery after simple crush injuries of nerves such as those produced accidentally in the operating theatre, by crutch injuries, or compression during sleep Experimental evidence *of the degrees of recovery has* been given by Gutmann (19) for the function of spreading of the toes of the rabbit following vestibular stimulation. When the peroneal nerve which provides the





17 Recovery of knee jerk by rabbit after injury to 2 of the 3 branches
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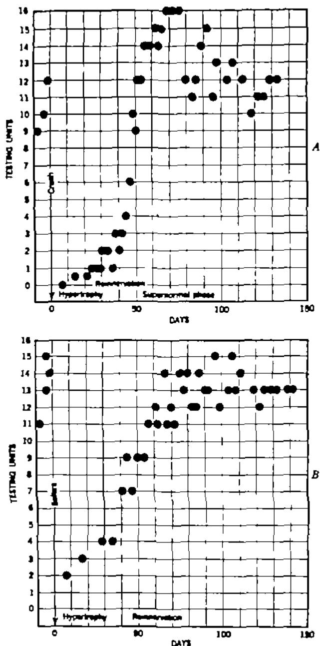


Fig. 17 Recovery of knee jerk by rabbit after injury to 2 of the 3 branches of the crural nerve The upward jerk of the leg is measured in arbitrary units *A*, nerve crushed with smooth forceps after some increase of response due to hypertrophy of the muscles innervated by the intact third crural branch there is rapid regeneration and a supernormal phase. *B* after neurotmesis the hypertrophy and recovery due to regeneration are continuous and there is no supernormal phase Data supplied by Mr D Barker

motor path for the reflex is interrupted by crushing with smooth forceps the spreading of the toes begins to reappear very shortly after the return of fibers to the muscle and increases rapidly in amount actually passing through a supernormal phase before returning to normal (Fig 15) A supernormal phase was also found by Barker and Young (5) studying recovery of the knee jerks of the rabbit following interruption of both its sensory and motor pathways by crushing part of the crural nerve (Fig. 17) The part of the nerve and muscle left intact was by itself at first able to produce only a minimal knee jerk then became hypertrophied so that when recovery occured also in the other muscles the total knee jerk was at first abnormally large

Regeneration after Severance of Nerves. Neurotmesis

Regeneration is very much less complete after a nerve has been cut across than when the axons alone are interrupted by crushing (Fig 15) Seddon (60) has suggested that the term "neurotmesis" be used for lesions in which the whole nerve including the tubes and other supporting tissues is interrupted as well as the axons. The process of degeneration in the peripheral stump is identical, however the nerve is interrupted The differences between the results of axonotmesis and neurotmesis lie in the events at the region of injury itself and can be studied by examining the sequence of events in a small nerve of the rabbit, severed with a single scissors cut in such a way as to leave the two stumps separated by only 0 5 mm A blood clot forms within this space and the organization of this clot is of great importance for the regeneration Weiss (79,80) has shown that during the third and fourth day after operation the fibrin of the clot becomes digested in such a way as to form strands if there is light tension along the axis of the nerve the strands will be oriented mainly along this axis providing as it were bridges between the two stumps (Fig. 18)

The first cells which grow along these bridges emerge mainly from the *peripheral* stump Nageotte showed long ago (48 49) that the Schwann cells can emerge from the cut end of a severed stump forming a tissue which he called a schwannoma or peripheral glioma. Such strands or "ghost nerves" (89) reach as much as 2 cm. beyond an isolated peripheral stump especially if they are able to grow along suitable surfaces Tissue culture experiments have also shown

that cells wander out from degenerating nerves but not from cultures made with normal nerve (1) There is no doubt therefore of the existence of these migratory cells Denny Brown (11) however



Fig. 18. Region of union between stumps of rabbit nerve severed 5 days previously and united by means of clotted cockerel plasma. The central stump contains nerve fibers (*ax*) vacuolated at their lower ends. From the peripheral stump columns of Schwann cells (*S*) are seen growing along the acellular strands of the fibrin clot (*f*) Bodian and Masson stains.

has recently suggested that they are not Schwann cells but a special type of fibroblast, the neural fibroblast. His observations were made on nerves of cats which had been severed within the perineurium the bundles being first pulled out with forceps through a slit. A very

great proliferation of cells, which seemed to him to be the fibroblasts of the perineurium, followed this procedure The perineurium undoubtedly can proliferate very rapidly after a nerve has been severed but it must not be assumed that its cells provide the whole

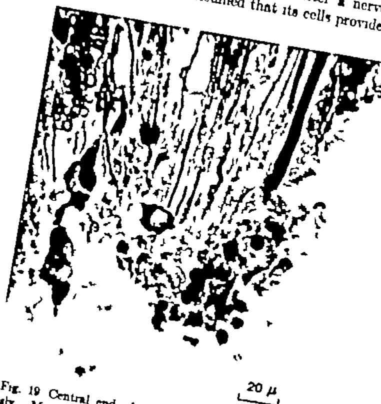


Fig. 19 Central end of a rabbit nerve cut 2 days previously Material has poured out from the end and divided into lumps of various shapes Bodian stain

of the outgrowth. In the nerves examined by Denny Brown the nerve ends were undoubtedly severely damaged by his method of pulling out the nerve and the proliferation of Schwann cells seems to have been reduced or absent. It is certain that under more usual conditions a special type of cell emerges from the cut peripheral stump (37,53) These cells are not easy to distinguish individually from fibroblasts but they have a characteristic habit of sticking side by side and hence growing in columns (Figs 20 and 21) Fibrocytes are nearly always separated from each other and moreover are



Fig. 20



Fig. 21

Fig. 20 Region of union between stumps of rabbit nerve united 5 days previously with cockerel plasma. Axons (*ax*) with vacuoles (*v*) are coming into contact with columns of Schwann cells (*s*) proceeding from the distal stump *f* remains of fibrin clot. Note that the nuclei lie mainly in the peripheral parts of these columns, having been derived from the distal stump Bodian and Masson stains.

Fig. 21 Region of union between stumps of rabbit nerve united 5 days previously with cockerel plasma. New nerve fibers (*ax*) are growing along the surface of the columns of Schwann cells (*s*) which can be traced to the tubes (*t*) of the distal stump Cell *f* is probably a fibrocyte Bodian and Masson stains.

usually plumper and shorter than the Schwann cells which may reach very great lengths especially as seen in tissue culture No one who has seen typical Schwann cell columns either in histologic preparations or *in vitro* can fail to recognize a characteristic tissue Denny Brown could not convince himself that the modified Schwann cells which remain in a degenerated peripheral stump have any connection with cells in the scar region. But his conditions were peculiar others have been convinced that the columns of cells uniting the cleanly severed ends of a nerve are derived from the Schwann cells which have multiplied and become migratory (Figs. 23 and 24) Whether these special cells are better called neural fibroblasts and whether they produce collagen are important questions for the embryologist and biochemist. For the study of the repair of nerve it is important to recognize that they exist as a special type of cell wandering out in columns from the peripheral stump We shall continue to call them Schwann cells it would be most unwise to alter this now classic practice without further evidence

They can be seen from about the third day moving along the strands of the fibrin clot uniting severed nerve stumps Cells emerging from neighboring tubes may stick together producing a lattice of strands reaching out toward the central stump (Fig 20) No doubt, some similar cells move from the central stump downward but it is very clear that this is not the main source of the Schwann cells, as has sometimes been suggested. In the early stages there are always more cells in the peripheral than in the central part of the union scar (Fig. 20) Perhaps if rough handling of the central stump at operation produces retrograde degeneration of the axons then central Schwann cell outgrowth may become vigorous for these cells only become migratory when the axon to which they are attached collapses.

OUTGROWTH OF AXONS ACROSS THE UNION SCAR

When a nerve has been severed by a single cut there is little or no retrograde degeneration. The central tips of the axons swell and the axoplasm may emerge from the cut end of the tube as a heterogeneous mass, presumably showing active movements during life (Fig. 19 page 194)

Some parts of this mass break off and form isolated fragments and rings which disappear but from other parts or from the portion

of the axon within the tube new streams of axoplasm proceed forward across the scar Often the axon becomes vacuolated and its substance splits up into sheets against the sides of the terminal portion of the tube in a manner similar to that seen after axonotmesis (page



Fig 22 New nerve fibers at entrance to distal stump 5 days after union of stump of divided rabbit nerve with cockerel plasma. One of the fibers divides into 5 branches. Bodian stain.

183) The result is that the original fiber produces several new branches either terminally or a little distance within the central stump The new fibers continue over the surfaces of the Schwann cells which make up the network in the scar and are thus led back into the old tubes of the peripheral stump (Fig 21) Before entering the latter each fiber may branch several times (Fig. 22) increasing the chances that it will reach a suitable channel. Reinnervation of the degenerated tubes is thus essentially similar to that found after

axonotmesis, but the number of fibers in each peripheral tube is far smaller when the nerve has been severed.

The processes which produce effective union of the two stumps are therefore outgrowth of (*1*) Schwann cells from the peripheral stump and (*2*) nerve fibers passing along the surfaces of these cells from the central stump (Figs. 23 and 24). Probably some outgrowing axons pass across by other pathways, perhaps by growth along fibrin strands or fibrocytes, but we do not know whether any considerable number of connections can be made in this way. The evidence suggests that anything which makes for longitudinal orientation of the fibrin clot, e.g. light tension, will promote growth of the Schwann cells and of the nerve fibers. Lateral tensions and intercurrent invasions of fibroblasts and blood vessels (Fig. 24) will divert Schwann cells and nerve fibers and reduce the success of the suture. But it must be understood that we still know too little of the processes which go on between the ends of a recently united nerve to justify dogmatism. It is to be hoped that our successors will acquire further knowledge of these processes and the ability to control them. The best hope of radical improvements in nerve surgery is by control of the events during the first few days after nerve suture.

Nerve Grafting and Other Means of Bridging Nerve Defects

The activity of the Schwann cells on which union between nerve stumps ultimately depends is limited in effectiveness to a very short range. The cells can migrate over a distance of as much as 20 mm., perhaps more, but in practice only a gap of a few millimeters is crossed by a sufficient number of them to allow a good functional union. If nerve stumps are separated by a gap wider than this, the tissue between them will consist largely of irregular masses of fibroblasts through which new nerve fibers grow very poorly, if at all.

The proper apposition of suitable nerve tissue is therefore a first requirement of nerve surgery: damaged stretches of nerve must be cut away and the ends somehow brought together. Unfortunately it is not very easy to decide whether the damage to a given stretch necessitates its removal. The ideal is to suture only stumps in which the bundles have intact perineuriums and in which the endoneurial connective tissue is not abnormally increased. However, quite good

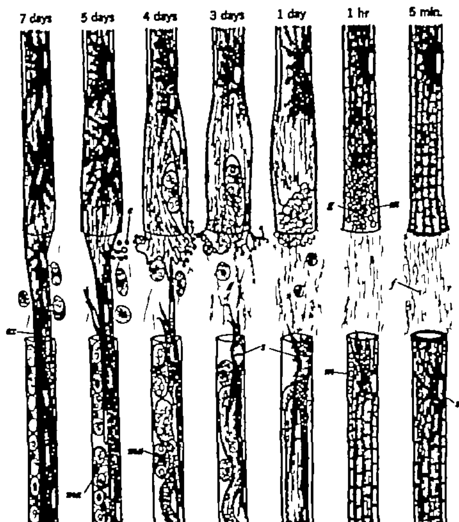


Fig 22. Diagram of changes following severance and suture of a nerve the stumps being joined by a fibrin clot (*f*) During the first hour after severance, the myelin breaks into droplets (*m*) for a short distance in both stumps and the axon also breaks into granules (*g*) The Schwann cells of the peripheral stump (*s*) begin to form migratory fibrous structures, and this process continues, with division of the nuclei, forming columns of cells growing out into the scar Meanwhile the axons and myelin of the distal stump break up and the tubes are invaded by macrophages (*ma*) The central stump axon swells, and the material pours from the end of the tube until some of it makes contact with the Schwann cell columns and is led back as a new axon (*ax*) into the peripheral stump Unconnected portions break off to form spheres and loops (*e*) The Schwann cells of the central stump first draw in their processes and then advance again over the outflowing axoplasm. The migratory Schwann cells of the peripheral stump also put out processes over the surfaces of the new fiber

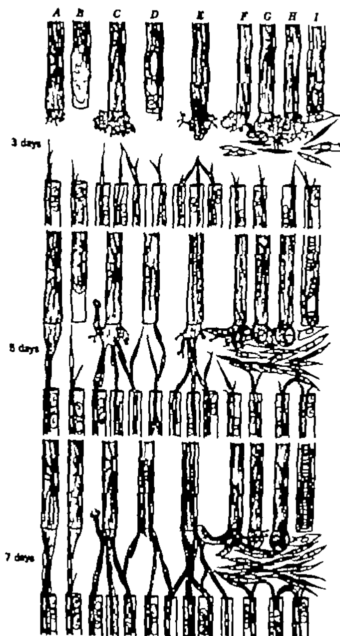


Fig. 24. Diagram of several nerve stumps on the third fifth, and seventh days after union, to show some of the variations which occur *A* a direct union, as in Figure 23. *B* some retrograde degeneration in the central stump and therefore delayed union. *C* the axoplasm divides into various streams in the scar and these make union with several distal tubes The same result is achieved in *D* by branching within the central tube and in *E* by branching at entrance to the distal stump All these unions are satisfactory but in *F–I* there is a lateral invasion of fibrocytes, preventing union of the stump, with resultant formation of giant clubs (*H*) or spirals of Perroncito (*I*)

recoveries may be achieved after sutures between stumps which on histologic examination are found to contain no intact bundles Holmes (34) discusses the allowable limits but they have not yet been finally defined and it is always wise to make resection as complete as possible The difficulty is that this may leave the stumps widely separated and there has been much discussion of methods of bridging the resulting gaps (6,54) Briefly the results of these studies are that nerve grafts are of value only in a certain limited number of cases in man, large nerve trunks especially should wherever possible, be repaired by mobilizing and bringing the ends together The limits of legitimate stretching of nerve are probably narrower than is supposed (31,32,72) indeed it is doubtful whether the nerves actually increase in length at all since silver clips placed on them do not move apart.

No methods of using heterografts or homografts taken from other animal or human subjects whether fresh cooled or preserved in alcohol or other ways have proved successful in man (5a,52 63 72a) The grafted pieces may survive in animals (9,39,56) but in man they fail to survive as conducting paths and no effective innervation is possible through them. Such methods should not be used further until means of controlling the reaction between host and donor tissue have been found

Autografted pieces of nerve survive well however especially if they are thin. Seddon *et al* (64) found that several strands used as a cable graft to repair a median nerve had survived well and become innervated there had been no effective recovery in this because for technical reasons there was imperfect union with the peripheral stump It is very difficult to obtain sufficient pieces of cutaneous nerve to equal the cross section of a major limb nerve Where it has been possible to overcome this difficulty promising results have been obtained with cable autografts In a certain number of cases, in which several major nerves have been damaged beyond possibility of repair by direct union it may be justifiable to sacrifice one nerve the ulnar to repair the median and radial Such full thickness autografts seem to survive well and provide another promising method (61) Autografts are especially effective in small nerves such as the facial (4) or nerves of the hands (8 61) In such situations they often constitute the only possible means of repair and quite good results have been reported



Fig. 25 Human digital nerves subjected to experimental operation 20 days before amputation of the finger At left, nerve crushed with artery forceps The injury was severe and interrupted the internal arrangement of the nerve, but yet left reasonably good conditions for regeneration. At right, nerve severed and the ends tied with stitches The apposition is very imperfect and fibers from the central stump are not entering the distal stump. Formol fixation and Bodian stain.

SUTURE MATERIALS AND WRAPPINGS

A word may be said here of the methods for uniting nerve stumps. Sargent and Greenfield (59) and Guttmann (26) have shown that linen white silk or fine woman s hair are suitable materials for suturing epineurium. Catgut, or silk colored with dyes likely to set up a reaction should be avoided Fine tantalum wire has recently been advocated (72) It is essential that the epineurium should be sutured in any situation where the nerve ends are under tension but in certain places where there is little tension clotted plasma has advantages (65 74 90) This is especially true in the placing of small nerve grafts for instance in the hands, since it is often very difficult to make good stitch unions of small nerves (Fig 25) Such methods are also very convenient for use in experimental animals. Sleeves of

artery (81) or perineurium (11) have been advocated as a means of uniting nerves but their clinical possibilities are not proved

There has been much debate as to the advisability of wrapping nerves to prevent invasion of the site of suture by fibrous tissue Since as Denny Brown points out the perineurium is a very active source of fibrocytes this procedure resembles that of locking the

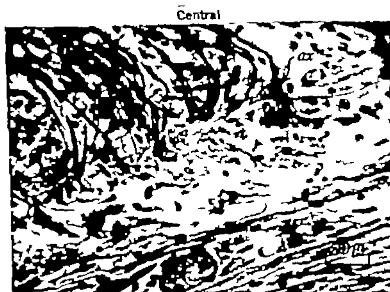


Fig 26 Central end of nerve severed 5 days previously Large masses of axoplasm (ax) have flowed out from the end and been diverted laterally by contact with a neighboring nerve bundle Bodian and Masson stains.

house with the villain inside Any material likely to constrict the nerve such as fascia lata is highly undesirable (44) Advantages have been claimed for the use of inert material, such as tantalum foil, in keeping the region of suture from forming adhesions with damaged tissue (72) but the value of this technic is still doubtful.

Union of Axons in Scar

The masses of axoplasm which form over the central end of a cut nerve do not always give rise to fibers which run peripherally Under some conditions the masses flow laterally making a remarkable web of axoplasm over the cut surface (Fig. 26) Sometimes neighboring

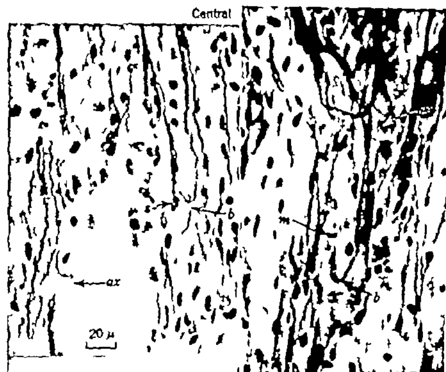


Fig 27 Two examples of bridges between axons in the scar region between stumps severed 7 days previously Note the large masses of axoplasm (ax) with the Schwann cells (s) on their surfaces. At m a Schwann cell is dividing. The bridges between axons are shown at b Bodian and Masson stains

masses undoubtedly fuse together for example in Figure 27 the axoplasm is well fixed and stained and shows no membrance dividing one fiber from the other Presumably in such cases impulses set up in one fiber must pass to the other and if one were a motor and the other a sensory fiber the former would stimulate the latter

Even when fusion is incomplete the materials of the axons lie very close to each other in suitable sections instances can easily be found in which axoplasmic surfaces are in contact (Fig 28) It seems very likely that these would function as synaptic junctions certainly electric disturbances in the one would affect the other

Granit *et al* (18) have shown that artificial synapses may be set up immediately after a nerve has been severed but the relationship of these to the fusions illustrated are uncertain. Prepara



Fig 23 Very close contact (pseudosynapses) between 2 fibers in scar between nerve stumps severed 7 days previously *Ax* are the two axons and *s* the region of contact Bodian and Masson stains.

tions of nerve stumps fixed during the first 24 hours after severance have not shown union or contact, since the outflows have not yet begun

It may be that these opportunities for stimulation of one fiber by its neighbors provide the basis for some of the pain felt in severed nerves (13) If numbers of motor and sensory fibers become connected in this way attempts at voluntary movement might produce pain Before accepting this view however it would be necessary to discover what proportion of these contacts and connections persist. They are numerous in the first two weeks but later the large masses *of axoplasm either become reduced or encapsulated by Schwann cells* and connective tissue to form the gigantic balls which Cajal described. Unions and contacts between fibers are less prominent after the first two weeks and it remains to be proved that they produce any clinical manifestations in sutured nerves or neuromas.

LATER STAGES OF REGENERATION AFTER NERVE SUTURE

The Schwann cells and nerve fibers cross the scar within the first week or two after suture During this time, collagen is also being *laid down giving strength to the union* (67a) Each nerve fiber becomes embedded in the Schwann cell strand to which it is attached presumably by virtue of the activity of the protoplasm of the cells of the strand

Collagen forms so rapidly around the whole as to give the suspicion that it is produced by activity of the Schwann cells (46) a possibility which seriously complicates the problem of their nature. From the surgical point of view it is important that the nervous connections between the stumps are mostly made during the first two weeks. *Later than this the union scar is heavily collagenized*, and it is doubtful whether it will admit further nerve fibers. Everything, therefore should be done to encourage nerve outgrowth during the early period Weiss suggests that *moderate* tension will help to orientate the strands of the clot. We have confirmed that when unions are made without tension the organization of the clot is largely transverse and the union is poor Possibly application of heat or other forms of treatment during this period would improve results, but this has not yet been proved

Maturation of the fibers in the peripheral stump is similar after nerve crushing and nerve suture but is slower and less complete in

the latter case Gutmann and Sanders (24) found that the typical bimodal distribution of muscle nerves had not reappeared more than a year after suture (Fig 15 page 188) Presumably the inevitable confusion in the union scar leads many fibers into false channels and if they reach tissues very different from their original ones they can not make connections Gutmann (20) has confirmed earlier evidence that cutaneous sensory fibers cannot connect with muscles the fibers may actually enter the old end plates but can make no proper con tact there On the other hand any motor fiber seems able to form contact with any striped muscle fiber but sympathetic postgangli onic fibers cannot unite with striped muscle (42,67) Such evidence and there is more of it, suggests that cholinergic nerve fibers unite only with tissues normally stimulated by acetylcholine and that adrenergic fibers act similarly

Functional Recovery after Nerve Suture

The final recovery is always less complete when a nerve has been divided and sutured than when the axons alone have been divided by a crush Thus Gutmann (19) never saw a case of full recovery of spreading of the toes of the rabbit after neurotmesis (Fig. 15) Barker and Young (5) found that recovery of the knee jerk of the rabbit after suture of the crural nerve was always incomplete and never exceeded 60 per cent of the normal In both studies some of the animals were followed carefully for long periods after the first appearance of recovery but very little gradual improvement was found. Clinical experience suggests that full recovery is not reached immediately there is reason to expect that after reinnervation muscles will hypertrophy with use and that functioning will become more effective. We must be cautious however about hoping for great improvements after the initial recovery there is no clear theoretical reason to suggest that improvement of function will continue after a certain limited time. The connections across the union scar are probably all made during the first two weeks. Those fibers which reach suitable end organs will then be stimulated to grow (page 189) Function will improve while they are doing so and as the muscles recover from atrophy and joints from stiffness These processes will no doubt take longer in man, with his long limbs than in laboratory animals but we must not expect sensational later improvement of function. Weiss (79) suggests that during development the first

successful pioneering fibers attract the addition of others. This may perhaps also be so in the union scar during early stages, but there is no evidence to suggest gradual later additions after recovery has begun

The extent to which false connections can be corrected is also rigidly limited Even a simple muscle nerve contains fibers of at least six different types since there is no 'neurotropic mechanism by which they are sorted into correct channels it is not surprising that recovery is always partial No doubt, branches from several different central fibers may enter each peripheral tube and only suitable ones will obtain that stimulation from the periphery which leads to maturation (page 189) thus providing for some mechanism of selection.

Many nerves contain motor fibers for various muscles and there is no evidence that later central readjustments can take place when false connections have been made Sperry (71) has performed decisive experiments on this subject and has surveyed the literature most carefully The widespread belief that central readjustment is possible in both sensory and motor fields is not justified by the facts, either in animals or in man Most of the alleged adjustments are not due to any real change in the pattern of activity of motoneurons, but to changes in the functional use of undamaged muscles. These facts have great importance for the development of proper methods of rehabilitation after nerve injury

EFFECT OF DELAYED SUTURE ON RECOVERY

It has long been known that there are cases in which some recovery has been obtained by nerve suture years after injury But it must not therefore be assumed that the results will be equally satisfactory whether the operation is performed early or late We have recently made a study of all stages of regeneration in order to discover if there are changes in the power of the process which would show us the optimal times for operations The power of the central stump to put out new axons is very great and does not decline appreciably if a nerve is left unsutured for a year (37) Gutmann (21) has shown by repeated crushing that a nerve may regenerate many times and show as quick and complete recovery the sixth time as the first.

The union between the stumps is made in the first instance by the Schwann cells which show a curve of activity with a maximum after

about 3 weeks followed by a slow decline (1) The peripheral stump is always able to receive new fibers even after years of degeneration but it is not easy to decide whether its powers to do so decline The young fibers appear to penetrate well along the walls of tubes somewhat shrunken and filled with Schwann protoplasm but the power of maturation and medullation may be impaired by delay A much more serious limitation to regeneration after delayed suture is the atrophy of the muscles and probably also of sense organs and skin.

The fibers of a denervated muscle gradually shrink and the connective tissue between them increases The empty end plates remain intact, and during the early stages are connected with the tubes of the degenerated nerve trunks New fibers arriving at this time can therefore enter directly into the old plates (Fig. 29) and the original pattern of innervation is restored (25) As atrophy proceeds however the channels become occluded new fibers then fail to enter old plates, but wander among the muscle fibers often forming remarkable longitudinal plexuses Contact may ultimately be established forming new plates which however are of very strange form and are irregularly distributed through the muscle so that the motor units must have a very different layout from the normal

In muscles left without nerve fibers for very long periods the fibers break up and disappear altogether such tissue cannot be reinnervated effectively The rate at which tissue is thus lost differs greatly in different animals and muscles being faster probably in the rabbit than in man. However everything suggests that muscles left for periods greater than six months begin to be seriously impaired No doubt, the degree of atrophy depends greatly on the treatment of the paralyzed muscle It has now been shown definitely that electric exercise of muscle retards atrophy (15,22,33 41a,68 69) The optimum conditions for stimulation remain to be discovered but it seems likely that repeated contraction against moderate resistance simulating the normal action of the muscle, may go far to protect it from atrophy (88)

Even with the most careful treatment, however a limb left for long periods without nerves becomes less able to recover disuse of joints is as serious as that of muscles and there may also be progressive changes in the skin. *Indications are therefore strongly in favor of early suture whenever possible* Unpublished analysis of end results of cases treated at the Nerve Injuries Centers in Great Britain

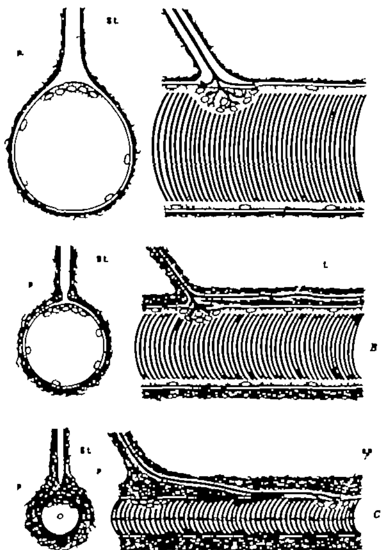


Fig 29 Diagram of changes in the relation of Schwann tubes to muscle fibers occurring as a result of progressive atrophy and fibrosis, which make reinnervation progressively more difficult. Transverse sections show the conditions before reinnervation longitudinal sections, the condition produced when the fibers return *A* very little atrophy has occurred, and the Schwann tube (S.t.) is in open communication with the space above the empty end plate (e.e.p.) returning fibers are able to branch in the old plate. *B* the *connection is restricted by fibrosis, and part of the stream of axoplasm escapes* to make a new fiber (e.f.) *C* connection with the old end plate (e.e.p.) is broken the fiber passes by making a new plate (n.e.p.) only by chance After Gutmann and Young (25)

as well as early assessment of cases in the States (72 72b) suggests that distinctly better end recoveries are made when operation is performed earlier than six months than when it is done later But it is not correct to suppose that the optimum time for suture is immediately after injury (91) The nerves are then soft and difficult to handle, it is difficult to recognize the exact extent of the damage and the Schwann cell activity is slight. Three weeks or a month after injury the extent of the lesion is better defined the epineurium is slightly thickened and easier to sew and the Schwann cell activity is near its maximum. It would seem that this is the optimum period for nerve suture. A primary exploration is usually desirable since the divided stumps may be brought into apposition and later definitive suture thus made easier But sutures of nerves undertaken at the time of excision of the wound commonly lead to unsatisfactory results *even under conditions where infection is no problem* (60a 72,91)

Decision as to Resection of Lesions in Continuity

Since recovery is much faster and more satisfactory after axon otmesis than after neurotmesis it is evidently of great importance after a nerve injury to decide whether the axons alone have been crushed. If the lesion approximates to a pure axonotmesis leaving the tubes little damaged, it will be advantageous to leave it for "spontaneous" recovery Unfortunately we have little information as yet about the nature of the tissue formed after various types of lesion which leave the ends of the nerve still in continuity It cannot be assumed that because there is continuity the lesion is a simple axon otmesis of the type here described. Lesions caused by traction on the nerve are especially likely to produce damage over a long stretch of nerve (31) Injuries of this type are especially common in the lateral popliteal nerve at the knee and in the brachial plexus and the problem of their repair remains unsolved Highet and Holmes (31) found that when the intact ends of the lateral popliteal nerve were brought together after long resections recovery did not take place because of the further damage to the nerve produced during stretching. Traction lesions may therefore be produced postoperatively as well as by traumatic injuries One of the most dangerous features of such lesions is that severe intraneural damage may exist without interruption of continuity Exploration of the nerve there-

ends are found separated suture will be performed at the optimum time If the nerve is in continuity the lesion can be examined and palpated and some estimate made of its severity Should it prove to be merely slightly swollen and its epineurium undamaged and with little trace of hardness within it we may suppose it to have suffered axonotmesis and many of its tubes still to be intact. This would justify leaving it without resection since optimal recovery can only be obtained if each fiber reaches its old end organ

If the epineurium is badly damaged and all the bundles feel hard with lumps of scar tissue we may decide to resect and suture immediately on the basis that although continuity has been retained conditions within the nerve will not be favorable for regeneration Unfortunately there are few aids available at present to help in this difficult decision. Electric stimulation and electromyography (78) may help by showing the presence of some intact fibers not revealed by neurologic examination. It is not impossible that methods could be discovered for stimulating either sensory or motor fibers and judging the nature of the lesion from their response but this has not yet been achieved Holmes and Zachary (38) have recently shown that much information may be obtained from nerve biopsy performed by taking a piece of nerve from below the lesion. Pieces so small that they are no loss to the patient may show by the size of the fibers they contain whether recovery is proceeding The same result can often be obtained by taking pieces of muscle, which nearly always contain small nerve trunks (7)

Rate of Regeneration

If during the exploratory operation it is decided that there is a considerable probability that much of the nerve has suffered only axonotmesis no resection will be performed. It then becomes of first importance to watch for the recovery in order to confirm the diagnosis Should the latter prove faulty resection and suture must be undertaken subsequently before it is too late It is here that we have perhaps least of all to guide us the decision obviously rests upon calculations based on the rate of regeneration and of this we know far too little especially in man. The subject is made very difficult by the fact that the term "rate of regeneration may mean many different things (23,85) We can distinguish first the rate of advance of the axon tips down the nerve This takes place very much

faster than has generally been supposed. After nerve compression in rabbits the tips appear in the distal stump after five days and advance downward at 4.5 mm per day (15a,23) Observation of the fibers in nerves crushed experimentally in man before amputation shows a similar rate Clinical observations (14 75) have also suggested a similar rate for the advance of axon tips We may therefore regard this as well established

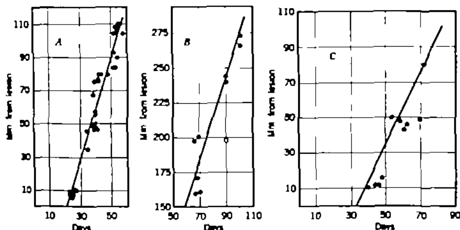


Fig 31 Three estimates of the rate of nerve regeneration in the rabbit (23) *A* time in days for recovery of spreading of the toes after crushing the peroneal nerve (the motor pathway for the reflex) at various distances from the muscles concerned the recovery advances at 3 mm. per day *B* time for recovery of sensation in the toes after crushing the peroneal nerve at various distances the rate is 3.1 mm per day *C* recovery of spreading of the toes, as in *A* after severance and suture of the peroneal nerve the rate is 2 mm. per day

After a good nerve suture in the rabbit the nerves appear in the distal stump 7 days later and advance down it at 3 mm. per day This slower advance applies to their progress through the whole peripheral stump and is an important difference between neurotmesis and axonotmesis Assuming similar rates in man, we can calculate the time of arrival of fibers after a given lesion. But the arrival of axon tips does not constitute a full regeneration of nerve. For this to occur the fibers must grow and medullate to a degree which enables them to produce normal function This process of functional completion of the fibers may move down the nerve at a very different rate from the advance of axon tips indeed it might

even conceivably move up the nerve (page 190) Moreover the degree of maturation necessary to produce function may well vary according to the distance of the lesion from the muscle, small fibers might suffice to conduct adequately for one activity over a short stretch but not for a longer stretch or a different activity

There is therefore no expectation that we shall find a "rate of regeneration," constant for all nerves, nor even for one function in any single species However investigations of the rate of apparent advance of functional completion have been made in the rabbit,

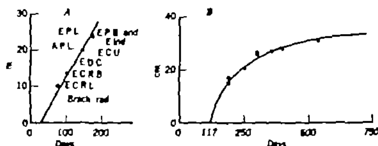


Fig. 32 Rates of regeneration in man (67) *A* recovery of the muscles following axonotmesis of the radial nerve recovery advances at a steady rate of 1.72 mm. per day *B* another case diagnosed as axonotmesis, in which the rate of recovery is not constant.

both for sensory and motor fibers essentially by watching for the times of recovery after lesions at various distances from the end organ (Fig 31) Again the rates are greater after axonotmesis (about 3 mm./day) than after neurotmesis (2 mm./day) Over the distances used the rate appears approximately linear but there is no guarantee that this would be also true in longer nerves the work of Seddon *et al* (66) shows that in man "the rate of recovery falls off progressively as the process moves towards completion It can, however, be regarded as constant over moderate ranges of time and distance."

They studied the time of reappearance of function in the muscles innervated by the radial nerve (Fig. 32) and, according to their classification the rate after axonotmesis was 1.5 mm., after neurotmesis 1.6 mm. per day From this it is clear that their criteria for the two conditions cannot be similar to those revealed by histologic study (page 211) Further work along the same lines should prove

most fruitful. There can be little doubt that it will show rates of advance of functional completion approaching 2 mm per day after true axonotmesis.

HOW LONG TO WAIT FOR RECOVERY WITHOUT RESECTION

Even without further information, these facts provide criteria by which to decide how long after a presumed axonotmesis one should wait before concluding that the diagnosis was faulty Obviously as early a decision as possible is important, so that if resection has to be performed it shall not be unduly delayed We can safely say that if the axons alone have been interrupted the fibers will cross the crushed region (assuming it to be not longer than 2 cm.) in 14 days at the outside and that thereafter they will advance down the peripheral stump at 3.5 mm. per day This leaves a wide margin for error No really satisfactory methods are known for detecting the first appearance of fibers at end organs but muscle biopsies have proved very promising (7) and biopsy of small pieces of nerve is not harmful to the patient and may show much (38) Electromyography (78) should serve to show the appearance of the first signs of motor function soon after arrival of axon tips Finally Tinel's sign though much disputed evidently depends on the progress of axon tips down the nerve it may yet prove useful in making the decision (40 47)

By a suitable calculation it should be possible to decide in each case the time at which some chosen sign is expected to make its appearance Regeneration after true axonotmesis is a very steady and regular process and unless some special circumstances are present we should await recovery with confidence and search urgently for the cause of any delay Allowing a good margin for unknown factors it should be the policy to operate again where recovery is unduly delayed In the past there has been a tendency to hopeful (or hopeless) optimism about the appearance of recovery as if the process of regeneration was highly variable and undependable Probably this is due to the fact that the nerve lesions encountered are so variable, and that many cases of lesions in continuity are more severe than they seem and involve more than a mere axonotmesis We do not know enough to be certain of the wise procedure to adopt in such cases It may be that some of them will

recover better by being left alone than after resection and suture (45a) But in other cases the nerve may be full of scar tissue and provide most unfavorable conditions for the fibers At least we should recognize that if regeneration does not occur at the time indicated by the known rates of regeneration after axonotmesis some block exists in the nerve and it is necessary then to consider the possible further alternatives

The overriding consideration in dealing with nerve injuries is that in the course of every week of delay the nerves, muscles and joints are becoming less and less able to recover We can continually attempt to conserve them, but cannot expect miracles from the physiotherapists Moreover with each week of delay not only the tissues but also the morale of the patient is suffering It is necessary therefore to use every effort to calculate as carefully as possible the time at which the patient should begin to have the use of his members and continually to adapt our ideas if this does not occur at the expected time

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The Use of Antibiotics in Surgery

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Introduction

The discovery and introduction of penicillin has changed profoundly the prognosis and management of a great number of surgical conditions. Surgeons often stress the fact that it has not altered basic surgical principles and that it must be thought of as an adjunct to good surgery. While penicillin certainly should not be used as an excuse for poor surgery, its introduction has led to the acceptance of a number of specific procedures which would have been attacked as violating fundamental surgical principles only a few years ago. It is perhaps fair then to say that it has forced a more exact definition and a more precise application of these important principles. From a practical point of view, it has permitted many patients with pyogenic infections to recover without drainage or with drainage by aspiration only, who previously required extensive incision and prolonged drainage.

Penicillin has replaced the sulfonamides in the treatment of staphylococcic infections, such as osteomyelitis, carbuncles, meningitis, sinus thrombosis, pneumonia, and empyema, because it is superior to all other available chemotherapeutic agents for the eradication of most staphylococcic infections. It is the agent of choice in most hemolytic streptococcic infections, whether it be bacteremia, cellulitis, mastoiditis, or puerperal sepsis. It is also the agent of choice in infections due to clostridia, anaerobic streptococci, gonococci, Bacillus anthracis, and Vincent's organisms. The brilliant results achieved with penicillin have intensified investigation in the field opened by Dubos with the development of gramicidin, namely the use of substances derived from micro-organisms as therapeutic

agents in medicine. Considerable effort has been put forth by many investigators to develop other antibiotic agents, especially those active against the organisms which are not affected by penicillin. Although many other antibiotic agents have been described penicillin and streptomycin are the only ones which are generally available for systemic use. Tyrothricin and gramicidin are available for local use only being too toxic for systemic administration. Bacitracin, according to Meleney (57), is effective in the local treatment of many infections but these observations have not yet been widely confirmed because of the present limited supply of the agent. The following discussion, therefore, will be devoted mainly to the uses of penicillin and streptomycin in surgery

Penicillin

Penicillin is a mixture of substances which are the product of the growth of the mold, *Penicillium notatum*. Fleming (24) while endeavoring to culture staphylococci, observed a zone of inhibition on the surface of the culture medium around a colony of penicillium which occurred as a contaminant. As a result of this observation he published a paper in which he suggested that material obtained by the growth of this mold be used to inhibit the growth of certain organisms in a mixed culture in order better to study other organisms not sensitive to the action of penicillin. This work lay dormant for twelve years until Chain Florey Gardner and co-workers (12) reported in 1940 the therapeutic usefulness of a substance produced by *Penicillium notatum* which they called penicillin. Adequate evaluation of penicillin had to await commercial production of the material This was accomplished under the pressure of war to a large extent in the United States, where the Committee on Medical Research under the direction of Doctor A. N Richards stimulated its production and organized wide clinical trials. With the purification of penicillin, it was found that there were several forms of the antibiotic these were designated as penicillin F G K, and X in the United States, and as penicillin I II III etc., in Great Britain (17) Most commercial penicillin contains not less than 90 per cent of penicillin G unless otherwise labeled.

While all forms of penicillin are active against some bacteria, they vary somewhat in their effectiveness against many given strains. Certain cases of subacute bacterial endocarditis which have not

responded favorably to the mixed penicillin have responded to penicillin X. Penicillin is standardized in terms of pure crystalline G The international unit agreed upon by Britain Australia, Canada, France, and the United States is now defined as the amount of the agent which has the potency of 0 6 μg of the sodium salt of penicillin G

The organisms listed in Table I are sufficiently sensitive to penicillin to warrant its use in infections caused by them. As is the case with the other antibiotics, there is considerable difference in the sensitivity between strains of the same species of bacteria, and there

TABLE I

Organisms Sensitive to Penicillin

Staphylococcus	Bacillus subtilis (hay bacillus)
Streptococcus pyogenes	Diphtheria group
Streptococcus viridans	Clostridia tetani, welchii, septicum, botulinum, etc.
Some anaerobic streptococci	Streptobacillus moniliformis
Pneumococcus	*Erysipelothrix rhusiopathiae* (erysipeloid swine erysipelas)
Gonococcus	Spirillum minus (rat bite fever)
Meningococcus	Spirochaeta (relapsing fever syphilis, yaws, Vincent's angina, Weil's disease)
Neisseria catarrhalis	
Micrococcus	
Sarcina	
Actinomyces	
Bacillus anthracis	

may be a difference in the same strain at different times. An increase in the resistance to the action of penicillin is apt to occur if therapy is inadequate. *In vitro* it is possible to increase the resistance of some organisms many times Generally penicillin is ineffective against the gram negative rods furthermore, it appears to have no influence on the course of the virus diseases, although it may assist in the prevention of certain complications due to bacteria. It is of interest that penicillin in very large doses has a protective effect in mice against certain bacterial endotoxins (58)

In chest surgery it has proved of value in both prophylactic and curative treatment of many empyemas and lung abscesses Bronchiectasis responds less favorably to the drug but often the amount of sputum can be reduced greatly (see Fig. 1) Although it is ineffective against the colon group of organisms, it has been bene-

ficial in the treatment of experimental peritonitis due to fecal contamination, and seems to be of value in the treatment of clinical peritonitis (13,22) Extensive clinical trial of the drug has been made in the treatment of contaminated war wounds, and the results obtained in both soft tissue wounds and in compound fractures have been very gratifying It may exert a beneficial influence in the treatment of gas gangrene. Murphy LaBocoetta, and Lockwood (60) have reported favorably on its use in cutaneous anthrax.

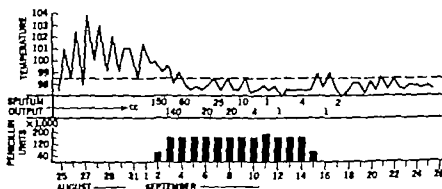


Fig. 1. Response of a 16 year old boy with bronchiectasis to penicillin therapy

Penicillin is now well established in the treatment of many postoperative complications. Infectious pulmonary complications generally respond well to its administration, and many types of urinary tract infections can be cleared up by the use of this drug. Surprisingly enough parotitis has not responded very favorably despite the fact that staphylococci are the commonest causative organisms

In the various surgical specialties penicillin has found so many fields of usefulness that only the major ones can be included in this chapter

DISTRIBUTION TOXICITY, AND ROUTES OF ADMINISTRATION

Penicillin is readily soluble in water, either in the form of its sodium or calcium salt. For this reason, it may be injected into, and absorbed from, the subcutaneous tissues and muscle. It may be given intravenously by continuous drip, or in divided doses Follow-

ing a single intravenous injection, the blood level rises rapidly to a maximum and then gradually declines so that at the end of 2½ to 3 hours the drug can no longer be detected in the blood, although it may be found in the urine. After subcutaneous or intramuscular administration of 5,000 to 40,000 units, the blood level reaches its maximum in about ½ hour, and then subsides to a negligible level in 2½ to 3 hours.

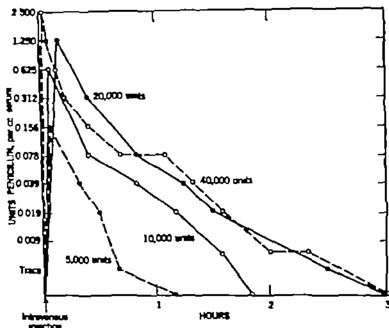


Fig 2 Penicillin concentration in serum following various doses (70)

Representative curves from a paper by Rammelkamp and Keefer (70) are presented in Figure 2. While on theoretic grounds continuous administration might seem necessary most clinicians have administered it in divided doses. It is generally given intramuscularly as this route causes less pain than the subcutaneous one and does not require skill in intravenous puncture. In most institutions it has been given at 3 hour intervals, although in the desperately ill a 2 hour interval has been employed. The blood levels are uniformly low in comparison with the doses administered. According to Herrell, Nichols and Heilman (37), a level of 0 96 unit per

cubic centimeter was obtained following intramuscular administration of 50,000 units At the Hospital of the University of Pennsylvania, the administration of 12,500 units intramuscularly gave serum levels of 0.3 to 0 4 unit per cubic centimeter Levels as low as 0.01 unit are detectable by the cup-plate method.

Penicillin diffuses from the serum into the erythrocytes but according to Rammelkamp and Keefer (70) the amount is limited to about 10 per cent of that present in the serum

The drug does not diffuse into the cerebrospinal fluid in normal individuals (1 70 71) It may be administered intrathecally, after the injection of 10 000 units by this route, it could be demonstrated in the fluid for at least 24 hours, but it had completely disappeared in 48 hours Rosenberg and Sylvester (74), however reported that penicillin may diffuse into the cerebrospinal fluid in the presence of acute inflammation in the meninges. This, however was not true of patients with syphilis of the central nervous system studied by Herrell (34)

The diffusion of penicillin into saliva was reported by Abraham, Chain, Fletcher Gardner *et al* (1) This was confirmed by Struble and Bellows (79) but was not confirmed by Rammelkamp and Keefer (70) The concentrations are apparently lower than those found in the blood.

The drug diffuses rapidly into the peritoneal cavity according to Miller and Foster (59) The concentration of the drug in the peritoneal cavity exceeded the concentration of the material in the blood Under the conditions of Miller and Foster's experiment, penicillin appeared in the peritoneal cavity 5 minutes after an intramuscular injection.

Herrell (34) believes that the diffusion of the drug into the pleural space is much less rapid. This opinion is based in part on the fact that the drug remains in the pleural space for a considerable time after it has been introduced there

Herrell Nichols, and Heilman (37) reported that the drug diffused into the joint fluid with or without inflammation, and reached a concentration equal to about one-half of that found in the blood

That the drug diffuses through the placenta of pregnant women and reaches the fetal circulation was established by the studies of Herrell *et al.* (37) and of Woltz and Zintel (87) The latter were

also able to demonstrate it in the amniotic fluid. In some of the earlier investigations it appeared that penicillin was not excreted in tears but with larger doses Struble and Bellows (79) found that some of it was excreted in this fashion and that it also gained access to the aqueous humor In the treatment of corneal ulcers and conjunctivitis, the drug should be employed systemically as well as locally

According to Herrell, penicillin is not excreted in pancreatic juice although it has been found in pancreatic tissues by Strubel and Bellows 1 hour after injection. These authors also found it in the liver heart, kidney lung, voluntary muscle, adrenals spleen, and small intestine.

For intrathecal infections susceptible to the action of the drug, 10,000 units may be injected by lumbar puncture, cisternal puncture or by ventricular tap The administration of 50,000 units by intra ventricular injection has been reported to produce severe circulatory collapse and convulsions in some patients (43)

EXCRETION

The kidneys are the principal route by which the drug is excreted. Various authors (34) have reported the recovery in the urine of from 40 to 99 per cent of the injected amount most investigators recovering between 50 and 60 per cent. The concentration of the drug in the urine may reach 120 units per cubic centimeter With most of the sulfonamides it was necessary to keep the urine volume high in order to prevent precipitation of sulfonamide crystals. With penicillin, however there appears to be no danger of precipitation and it is possible to reduce the fluid intake in order to obtain a high concentration of this substance in the urine Penicillin is excreted into the bile, as reported by Abraham *et al.* (1) the bile concentration is lower than that ordinarily found in the urine but it may be higher than that found in the blood

TOXICITY

One of the most remakable things about penicillin has been the absence of serious toxic effects. Keefer's (46) comment on this point is Tens of thousands of patients have now been treated with the drug, and yet as far as is known, penicillin has never caused a

single fatality Furthermore, no harmful effects have been observed on the liver kidneys, or hematopoietic system, the organs which are usually most susceptible to damage by chemotherapeutic agents."

Urticaria is encountered in from 2 to 5 per cent of the patients receiving the drug. The urticaria is ordinarily mild and therapy need not be discontinued. If given intravenously, it occasionally produces a local phlebitis Several patients to whom we have given the drug have developed abdominal pain shortly after injection. The pain is usually cramplike, and may be severe. Diarrhea is occasionally produced To what extent these manifestations are due to penicillin itself and to what extent they are due to impurities in the commerical product it is difficult to say

ATTEMPTS TO CIRCUMVENT THE NEED FOR FREQUENT OR CONTINUOUS PARENTERAL ADMINISTRATION

A patient must usually be hospitalized for parenteral administration of penicillin. With the use of the drug spreading to the treatment of minor ailments this restriction has become increasingly burdensome and a search for easier modes of administration was made. This search has followed three main lines (1) oral administration (2) retardation of excretion (3) retardation of absorption. Preliminary experiments in England and in this country showed that oral administration was very unsatisfactory with the dosages employed parenterally The drug was absorbed in the upper portion of the small intestine, but it was destroyed to a considerable extent in the stomach by the gastric acids, and also in the lower portion of the intestinal tract by organisms of the colon group, some of which elaborate penicillinase, an enzyme capable of inactivating the drug.

Many attempts were made to get the material through the stomach in enteric coated capsules but no coating was found which would reliably release the drug in any particular part of the intestinal tract. Various substances were added or given ahead of time, to reduce gastric acidity however if large enough doses were given by mouth satisfactory blood levels could usually be obtained without any special vehicle. The ratio of oral to intramuscular dosage which produced equivalent blood levels was of the order of 10 1 Finland et al. (23) and Ross et al. (75) have successfully used the oral route in the treatment of pneumonia.

p-Aminohippuric acid has been administered in an attempt to

retard the excretion of penicillin. The results have been reported by Beyer *et al* (6) More recently caronamide has been used for this purpose.

Various methods were employed to depress the rate of absorption from subcutaneous or intramuscular sites of injection. Trumper and Hutter (81) reported the application of cold to the injection site. Fisk, Foord, and Alles (25) combined the drug with adrenalin. Parkins et al. (66) combined the drug with gelatin and a vasoconstrictor and found that absorption was delayed sufficiently to maintain the blood level for 6 to 8 hours following a single intramuscular injection. A vehicle of peanut oil and beeswax was recommended by Romansky and Rittman (73) and was given considerable trial by Kirby *et al* (52) The penicillin blood level thus administered may be prolonged for at least 12 hours following injection. This method has had a more extended clinical trial than any of the others, chiefly in the treatment of gonorrhea. We have hesitated to give long series of injections of this material routinely fearing that in an occasional patient the vehicle might be poorly tolerated.

Sterile abscesses containing an oily nucleus have occasionally been found in patients who have received various hormones suspended or dissolved in oil. Months or even years sometimes elapse between the injection and the development of such abscesses.

USE OF PENICILLIN

In Staphylococcic Septicemia

To emphasize the tremendous value of penicillin in the treatment of staphylococcic septicemia, it is worth considering the treatment of this condition prior to the discovery of penicillin. In 1930 Lewis taught that the mortality in this disease was 90 per cent. In some cases in which the blood would temporarily become sterile, localized infections later appeared and added to the mortality Many attempts were made to develop an immune serum useful in the treatment of staphylococcic septicemia, but it was not until Julianelle (44) introduced an immune rabbit serum that any significant progress was made. With this material the mortality was reduced to about 55 per cent. Bacteriophage was then used, and with it the mortality is reported to have been reduced to below 40 per cent in some series.

The sulfonamides which have proved so effective in the treatment of streptococcic septicemia, did not significantly alter the course of staphylococcic septicemia. In the early series, the mortality of penicillin treated staphylococcic septicemias was about 30 per cent. In these early cases the drug was administered in inadequate amounts because the available supply was limited. In many instances, penicillin was utilized only after unsuccessful trial of the sulfonamides In staphylococcic septicemia with early and adequate amounts of penicillin the mortality has been reduced to between 10 and 15 per cent. The disease is relatively rare, so that it is difficult for a single observer to collect more than a short series of cases, and now that the drug is available to the profession at large it is even more difficult to concentrate the experience The desirable daily dose of the drug has not been adequately established but most clinicians favor large dosage (500,000 to 1,000,000 units) The need for surgical drainage of localized collections which might seed bacteria into the blood remains.

Since subacute bacterial endocarditis is primarily a medical disease, it will not be considered in detail here.

In other types of septicemia penicillin has not been tried as adequately because the sulfonamides have proved so effective.

However in reviewing the experience with penicillin, Herrell (34) collected records of a series of 16 cases of streptococcic septicemia with 15 recoveries 21 pneumococcic infections with 17 recoveries, and 14 neisserian infections with 13 recoveries. Until the sensitivity of the responsible organism has been determined many physicians may prefer to employ both sulfonamides and penicillin. The clinical and bacteriologic response of patients with staphylococcic septicemia to penicillin is slower than that usually obtained with sulfonamide treatment of streptococcic septicemia. It may take from 7 to 10 days for the temperature to return to normal and 24 to 48 hours before any change can be detected It is important, therefore, not to discontinue treatment with the drug simply because the immediate response is unimpressive.

In Skin Infections

The need for penicillin in the treatment of the serious systemic diseases was so urgent that considerable time elapsed after its

introduction before it became available for the treatment of minor infections, furuncles and carbuncles, except when these lesions were localized in especially dangerous areas, such as the upper lip or nose

While life is seldom endangered by the ordinary furuncle or carbuncle the discomfort and inconvenience produced by these lesions is considerable. Recurrent furunculosis may incapacitate the subjects for months, as in the case of a physician treated at the hospital of the University of Pennsylvania in 1944. This patient had had many furuncles and carbuncles on his back, and had been more or less incapacitated for 8 months He had failed to respond to any of a variety of drugs. Penicillin, 100,000 units daily produced immediate improvement, and the condition rapidly cleared. In the treatment of an occasional furuncle or carbuncle it may be unnecessary to administer the drug systemically Some English workers have advocated applying it locally in ointment form. Perhaps a more effective maneuver is to inject the penicillin locally in and about the lesion. It has been our custom to dissolve the penicillin in a 1 per cent procaine solution This solution produces a temporary local anesthesia and has not been attended by any recognized deleterious side effects. In many instances the radical wide excision of carbuncles is no longer necessary if the lesion and the tissue immediately surrounding it are infiltrated with penicillin solution. A simple incision to provide drainage may suffice. For more severe lesions we prefer to administer the drug both locally and systemically In the experience of Altemeier and Helmsworth (3) even certain soft tissue abscesses arising in patients with osteomyelitis may be treated by aspiration and injection of penicillin.

Axillary furunculosis has always caused considerable disability in the past, especially among hospital personnel. The development of a furuncle in the axilla frequently marked the beginning of a siege of trouble. With the introduction of penicillin it is now usually possible to control the infection with one surgical drainage We have preferred systemic administration of penicillin in treating this particular disorder When dealing with large carbuncles penicillin should always be employed as a useful adjunct to surgery

In Cellulitis and Thrombosis of Carotid Sinus

Penicillin has also been most useful in the deeper soft tissue infections Facial infection associated with sinus thrombosis fre-

quently responds to this drug Herrell (34) collected reports of 8 such cases treated with penicillin, 7 of which recovered. In several of them there was a loss of vision on the affected side, but the fact that the patients survived seems remarkable in view of the uniformly poor prognosis which attended this condition prior to the use of penicillin.

In Ludwig's Angina

The sulfonamides have exerted a remarkably beneficial effect on the course of this disease. Penicillin has also been very effective, and we believe it is now the drug of choice. However we do not consider it improper to use both drugs pending the accumulation of further clinical experience. Tracheotomy is now seldom necessary except in the occasional neglected case.

In Acute Hematogenous Osteomyelitis

It is generally recognized that changes in the bone are not roentgenographically discernible in the early stages of acute hematogenous osteomyelitis. However even when the clinical response to penicillin is favorable, with a fairly prompt reduction in temperature and a subsidence of pain and tenderness subsequent roentgenography often reveals a mottling of the bone and this mottling may involve a considerable portion of the shaft. When these changes after penicillin therapy were first observed it was feared that a major portion of the shaft might sequestrate. However this has seldom, if ever occurred as a rule, after a period of many weeks, the mottling tends to clear so that surgical intervention is not required.

In the treatment of acute osteomyelitis it is important to remember that this is a disease which in the past has been attended by a considerable mortality especially in those cases in which the blood culture for Staphylococcus aureus gave a positive result. Wilson and McKeever (86) report a mortality of 12.2 per cent, and Kenney (49) a mortality of 23 per cent. Both of these series included patients who did not have a bacteremia. Brown (9) in a collected series of cases which included only those with a demonstrable bacteremia, found the mortality to be 35 1 per cent. Baker and Shands (5) in a similar group of patients, found the mortality to be as high as 70 per cent. Kenney employing the criteria mentioned above, collected

a series of cases and found the average mortality to be 51 per cent.

In a series of 19 cases of acute hematogenous osteomyelitis with blood positive on culture for Staph. aureus, treated in Philadelphia with penicillin and supplemented with surgery (when this seemed desirable), the mortality was only 5.3 per cent (85) Of the surviving 18 patients, 16 have shown no recurrences up to the end of 1 to 2 years. The one patient who died was infected by a Staph. aureus resistant to a concentration of 10 units of penicillin per cubic centimeter of blood.

In Chronic Osteomyelitis

In the treatment of chronic osteomyelitis with penicillin, three general methods have been employed. In the first, penicillin has been administered without any surgical intervention. In the second along with penicillin, a limited surgical procedure has been employed to establish drainage, with the removal of some obviously necrotic bone. In the third, penicillin is combined with an adequate surgical excision of the sequestra and diseased soft tissues The results obtained show very clearly that the third method is the best where it is anatomically feasible. White Zintel, and Lockwood (85) analysed their experiences with chronic hematogenous osteomyelitis and divided their cases into three groups (*1*) penicillin without surgery (*2*) penicillin plus inadequate surgery, (*3*) penicillin plus adequate surgery The best results were obtained in the last group

As might be expected the results obtained in the group of patients in whom the diseased bone and soft tissue were adequately excised were somewhat better than the results which Baker (4) obtained using sulfonamides and surgical excision. The wounds in 7 of the patients in the Philadelphia series, in whom a rather complete surgical excision was possible, were closed primarily, and in all 7 prompt healing occurred.

In Chronic Traumatic Osteomyelitis

The results obtained in the traumatic cases of osteomyelitis are similar to but on the whole somewhat less satisfactory than, those of hematogenous origin. This corresponds with the experience reported by Baker (4), who employed sulfonamides. It is again evident that if good results are to be obtained in a high percentage of cases surgical excision of diseased tissue must be thorough.

In Digital Osteomyelitis

Osteomyelitis in the fingers and toes may develop from extension of adjacent soft tissue infection. In the past, digits so affected were frequently amputated Recovery was so long delayed and so often resulted in partially disabled extremities that amputation was widely employed in the treatment of this disease The introduction of penicillin made it evident that a change in viewpoint was justified. Few soft tissue infections extended to the bone with penicillin therapy and early osteomyelitis often resolved itself In a series of 11 cases of digital osteomyelitis observed in Philadelphia, 8 healed without amputation, and in one of the others the drug was given an inadequate trial Greater experience is of course necessary before valid conclusions can be drawn.

Florey and Williams (28) reported a gratifying experience with penicillin in the treatment of infections of the hand in 1944. In a series of 40 such cases treated with penicillin the work days lost were reduced by 50 per cent, as compared with the control group

In Lung Abscess

In lung abscess, as is the case with most infections, the response of the disease is directly related to the responsible organism's susceptibility to the action of penicillin. Unfortunately, abscesses of the lung usually harbor a variety of organisms, some of which may be resistant to the action of the drug Occasionally, an early case has responded favorably without surgical drainage.

In a favorable case (Figs. 3 and 4) improvement was noted in several days and at the end of 30 days the abscess had largely healed In this case, the abscess developed in a 5 year old child subsequent to a tonsillectomy performed under general anesthesia. The abscess had failed to respond to sulfonamides and the child was seriously ill at the time penicillin therapy was started. A similar experience was reported by Florey and Florey (27), and Keefer *et al.* (48) have also had favorable results in certain cases of lung abscess treated with penicillin.

In Empyema

Earlier in this chapter reference was made to the fact that penicillin injected into the pleural cavity remained there longer than it did in other serous cavities. For this reason it seemed doubtful

that penicillin given systemically could reach the pleural cavity in adequate concentrations The local instillation of the drug into empyema cavities therefore appeared logical

Flippin and White (26) treated a number of patients with



Fig. 3. Post tonsillectomy lung abscess in a 5 year old boy before treatment with penicillin (54a)



Fig. 4. Roentgenogram of same patient 30 days later following systematic penicillin administration (54a) No surgical intervention was necessary

empyema by aspirating the pus and injecting a penicillin solution into the abscess cavity In about 50 per cent of their cases the infection was controlled and eradicated without other surgical help

These authors aspirated the abscess cavity daily and injected 25 000 units of penicillin solution into the abscess cavity Other investigators have had a similar experience (35) All are agreed that the abscess cavity must be emptied of its pus regularly and frequently If the cavity for any reason does not lend itself to emptying, prompt surgical drainage is indicated.

Unwarranted surgical delay is unwise If the cavity cannot be emptied of its pus or if after a trial of penicillin for a few days the patient does not improve, surgical intervention is indicated During the early stages of empyema when the mediastinum is mobile, there can be little valid objection to the introduction of penicillin into the pleural space When the response to this method of treatment is prompt and favorable surgical drainage can be deferred for a short time and in some cases avoided

Penicillin can be employed as an adjuvant to surgical drainage either of the closed or open type In closed drainage the cavity can be treated continuously with a penicillin solution (1,000 units per cubic centimeter) by tidal irrigation

Empyema in civilian life usually appears as a complication of pneumonia and is therefore much less frequent since the introduction of sulfonamides and penicillin in the treatment of pneumonia.

In Prevention of Empyema Following Lung Resection

White and co-workers (84) in 1944 studied a heterogeneous group of patients in whom lung resection was contemplated. Alternate cases were chosen for control The noncontrol subjects were given 150,000 units of penicillin daily for 7 days immediately prior to operation and for 7 days immediately after operation. While the benefits from the drug were unimpressive in those patients with carcinoma of the lung and pulmonary tuberculosis the results were encouraging in patients with suppurative lesions of the lung.

In this group of cases the incidence of empyema was 100 per cent among the controls and zero per cent among the treated cases. The postoperative temperature level was lower and the duration of fever shorter in the treated patients The penicillin treated group became ambulatory earlier and left the hospital sooner than the control group While subsequent study has shown that penicillin will not uniformly prevent the development of empyema after lung resection, it has certainly reduced its incidence.

The development of empyema subsequent to operations for the removal of foreign bodies from within the thorax has been substantially reduced by the use of penicillin according to d Abreu, Litchfield and Thomson (2), and Nicholson and Stevenson (63)

In Pericarditis and Mediastinitis

White and co-workers (83), in Philadelphia, obtained successful results in 3 patients with pneumococcic pericarditis. The drug was given locally in the pericardial cavity as well as systemically While it will be necessary to wait for further experience before we can fully evaluate the role of penicillin in pericarditis, it certainly appears to be the most valuable drug thus far available for infections due to organisms sensitive to its action If a gram positive coccus is recovered from the pericardial sac it would seem wise to start penicillin therapy immediately Penicillin sensitivity should be determined as early as possible, as a guide to further therapy

In mediastinitis it is frequently impossible to recover the offending organism early in the disease, but on the basis of probability we would recommend immediate institution of both sulfonamide and penicillin therapy In both pericarditis and mediastinitis relatively large doses should be employed—500,000 to 1,000,000 units daily The volume of penicillin solution introduced into the sac must be limited to avoid cardiac compression.

The removal of pus from the pericardial cavity by aspiration is just as important as it is in established empyema

In Peritonitis

Peritonitis may correctly be discussed under the headings of primary and mixed. Primary peritonitis is usually a specific disease mixed peritonitis is usually secondary to a lesion of a hollow viscus or an external wound. As a consequence, a combination of organisms cocci, and gram-negative bacilli is generally found in mixed peritonitis. Inasmuch as the gram-negative bacilli are unaffected by the presence of penicillin, mixed peritonitis might not be expected to respond to the drug. However animal experiments conducted at Bethesda, Md. by Fauley and co-workers (22) indicated that penicillin did lower the mortality in this disease. The authors prepared dogs according to a modification of Bower's technic (7) The appendix

was ligated at its base, and the mesoappendix was divided, the organ was thus obstructed and deprived of its blood supply In the control series, the mortality was 93 per cent In the penicillin treated group a number of deaths occurred among those animals in whom a fecal fistula had developed between the bowel and peritoneal cavity With these cases included, the mortality in the penicillin-treated group was 57 per cent.

The results of these experiments would indicate that the penicillin susceptible cocci played the more important role in the lethality of mixed peritonitis

In experiments conducted in the Harrison Department of Surgical Research at the University of Pennsylvania, under experimental conditions somewhat more severe than those embodied in the Bower technic, the mortality in the control group was found to be 94 per cent, whereas the mortality in the group treated with the penicillin and sulfonamide was found to be only 60 per cent. Further experiments in this series, involving the use of streptomycin are presented on page 255

Since the introduction of the sulfonamides, it has become difficult to evaluate new drugs or a combination of them in the treatment of human peritonitis because sulfonamide therapy was accompanied by a substantial decrease in the death rate in this disease. Consequently it has been our practice in the treatment of human peritonitis to employ both penicillin and sulfonamides. While this procedure was at first used empirically, more recently Kay and Lockwood (45) have reported the frequent occurrence of bronchial pneumonia in dogs with widespread peritonitis Penicillin may play a vital role in minimizing this pulmonary complication.

We have used relatively large amounts of penicillin (300,000–1,000,000 units per day) in the treatment of human peritonitis. After the critical stage of the disease has passed, the dose may be decreased. In recent cases, streptomycin has also been employed (page 256)

It is imperative that the source of contamination be excluded whenever possible, and that intraperitoneal necrotic tissue be removed. This principle was found essential in the treatment of peritonitis with sulfonamides, and we believe it remains important with penicillin. In the treatment of this condition with chemotherapeutic and antibiotic agents recognition must be given to the usefulness of whole blood, intravenous fluid, and other supportive measures.

In Compound Fractures

The war resulted in a great number of compound fractures. The efficacy of penicillin in the prevention of infection in this injury has been difficult to evaluate. Jeffrey and Thomson (42) and Furlong and Clark (29) reported an early series of 140 cases of compound fractures of the femur 70 patients in this series were treated with penicillin, the remaining 70 served as controls. The mortality in the penicillin series was 1 4 per cent, whereas the mortality in the control group was 8.5 per cent. Amputation was required in 2.8 per cent of the penicillin treated group and 8.5 per cent in the control series. It is interesting to note that in the penicillin treated cases amputation was not necessitated by infection. In one instance, injury to the femoral artery in Hunter's canal made amputation necessary and in the other case amputation was performed to remove a hopelessly damaged extremity

Cutler Morton, and Sandusky (15) reported the infection rates in a series of compound fractures. In the penicillin treated group the rate was 15 7 per cent in the control group 17.8 per cent. It would appear that penicillin limits the infection rather than eradicates it. In all of these experiments the dose of penicillin administered was perhaps too low, as judged by current thought and practice.

In Prevention and Treatment of Postoperative Complications

Postoperative Respiratory Complications Bronchopneumonia and atelectasis probably constitute the two most important postoperative respiratory complications They frequently occur together and it is often difficult to distinguish between the two diseases clinically It is well known that atelectasis predisposes the patient to the development of pneumonia. The responsible organisms in many of the bronchopneumonias are streptococci, staphylococci, and pneumococci. Since these organisms are usually susceptible to the action of penicillin, the drug has proved to be most helpful in the treatment and prevention of pneumonia. The importance of deep breathing, frequent change in position, and the expectoration of sputum has not been lessened by the introduction of penicillin. When a postoperative respiratory infection is suspected, penicillin should be started at once. While it has not seemed worthwhile to employ the drug prophylactically as a routine measure in all patients we have used it in this manner in groups of patients especially prone to the

development of such infections, for example, those with chronic bronchitis.

The mortality on the Surgical Service of the Hospital of the University of Pennsylvania from bronchial pneumonia was 69 per cent in the 4 years prior to the employment of sulfadiazine. With the use of sulfadiazine, the mortality from this disease fell to 9 per cent (72). We now regard penicillin which is more polyvalent and less toxic, as preferable to the sulfonamides in this field. When the response to penicillin is unsatisfactory, sulfadiazine is still employed.

Urinary Tract Complications. Penicillin is excreted in the urine and can be found there in relatively high concentrations. If the responsible organism is penicillin-sensitive, one may expect a good therapeutic response. However, if obstruction is present anywhere in the urinary tract, no lasting improvement is apt to be obtained until it is alleviated. Also, many of the urinary tract infections are caused by the gram negative bacteria, a group of organisms generally refractory to the action of penicillin. An exception, of course, is the gonococcus, for which the drug is especially indicated.

Postoperative Parotitis. While many of the infections of the parotid gland are caused by the staphylococci, penicillin has not proved to be as useful as was expected. No good statistical data on this subject have as yet become available to us. At present, it would seem the drug should be used if only to help localize the infection.

Thrombophlebitis. Penicillin has exerted a recognized beneficial effect only in those cases of thrombophlebitis in which there is a definite bacterial infection caused by a penicillin-susceptible organism. In cases of suppurative thrombophlebitis, the drug has occasionally been life saving.

In Ophthalmology

Penicillin has been found useful in the treatment of many types of conjunctivitis. It apparently limits the infection which may follow corneal trauma, and it may prevent corneal ulceration in severe infections of the eye. A detailed consideration of the use of the drug in ophthalmology may be found in the reviews by Dunnington and von Sallmann (20) and by Keyes (50). The general trend in penicillin therapy of most diseases is toward systemic administration of the drug, but in ophthalmologic diseases local instillation has proved especially useful. In a series of experiments conducted by Leopold

et al. (54) ulcers were produced in the rabbit by the use of a strain of gram negative bacilli. In these experiments penicillin solution applied locally to the conjunctiva was more effective in limiting or controlling the infection than systemic administration, thus giving the support of controlled experiment to the belief that in the treatment of conjunctival infection topical application of the drug is more effective than the systemic administration of it

In Otolaryngology

Many of the common invaders of the throat, middle ear mastoids and paranasal sinuses are susceptible to the action of penicillin. It may be employed prophylactically or curatively The drug has been used extensively and successfully in patients with otitis media to limit the infection and to prevent its spread to the mastoid cells Established acute mastoiditis ordinarily demands surgery although in certain cases the infection has subsided after penicillin therapy without surgery For a comprehensive discussion of this subject the reader is referred to the paper of Swanson and Baker (80)

In Gynecology

In the prevention and treatment of sepsis following incomplete abortion, penicillin has proved to be especially useful. Gonococcic infections of the genitourinary tract in women have frequently responded favorably to the drug. Gonococcic abscesses usually require drainage but in less extensive infection the diseases may clear with out operation when penicillin is used. Heretofore, spontaneous rupture of pelvic abscesses of gonococcic origin has been attended by a high mortality In these cases, Klingensmith (53) has employed penicillin intraperitoneally at the time of drainage and systemically in the postoperative period. The number of cases treated in this fashion is too small to permit statistical analysis but on clinical grounds the evidence is strong that the drug improved the chance of the survival.

In Cutaneous Anthrax

Murphy LaBoccetta, and Lockwood (60) reported 3 cases of cutaneous anthrax successfully treated at the Philadelphia Hospital for Contagious Diseases. In each of the 3 patients the lesion subsided

rapidly and did not recur Systemic anthrax, fortunately, is very rare in the United States, and we are not aware of any cases treated with penicillin.

In Gas Gangrene

In a series of 33 cases of gas gangrene treated with penicillin in the Italian Theatre, Jeffrey and Thomson (42) reported a mortality of 36 per cent. In one-half of the fatal cases death took place before penicillin had a sufficient time for a fair trial. Radical surgical excision of gangrenous tissue and gas gangrene antiserum were regularly employed so that it is difficult to evaluate the role played by penicillin. These authors observed that there was a latent period of 36 hours before the penicillin produced an evident clinical effect. From this it would seem that administration of the drug should be continued even when patients fail to respond promptly Cutler and Sandusky (16) report a series of 7 cases of gas gangrene treated with local and parenteral penicillin, with 1 death 5 of their cases received penicillin immediately after wound debridement, but nevertheless developed gas gangrene. With surgical removal of diseased tissue, gas gangrene antitoxin, and additional penicillin, all 5 recovered.

On the basis of present information, reported by North (64), it would seem wise to employ large doses of penicillin as an adjuvant to radical surgery and antitoxin in gas gangrene.

Streptomycin

The discovery of streptomycin by Schatz Bugie and Waksman (77) was made after prolonged and intensive investigation of the antibiotic properties of many organisms commonly found in the soil. Realizing that all virulent bacteria finally find their way back to the soil, and that these virulent bacteria were constantly disappearing from the soil, they reasoned that common soil bacteria probably produced antibiotic substances.

Streptomycin does not appear to have as wide a field of usefulness as penicillin. It does have a bactericidal effect against many gram negative organisms and mycobacteria which are resistant to the action of penicillin. In addition, streptomycin is somewhat active against the gram positive organisms, including the penicillin resistant Streptococcus faecalis and against a limited number of strains

of other streptococci, staphylococci, corynebacteria and diplococci. Streptomycin is useful in mixed infections because its field of anti bacterial activity is wide, and because unlike penicillin, it is not inactivated by the products of certain bacterial organisms, nor by purulent or nonpurulent body exudates which reduce the effectiveness of the sulfonamides. Streptomycin is not inactivated by serous transudates or normal tissue juices.

PRODUCTION AND PROPERTIES

Streptomycin is produced by the culture of a strain of *Streptomyces griseus* Streptomycin is an organic base soluble in water and dilute acids, but insoluble in organic solvents such as ether and chloroform. Alkaline copper (Benedict's reagent) is reduced when concentrations greater than 1,000 µg. of streptomycin per cubic centimeter are present in the urine. For clinical use, it is usually prepared as the hydrochloride or the sulfate salt of the base The activity of 1 0 Gm. of the free streptomycin base is roughly equivalent to 1,000,000 streptomycin units (Esch coli units) Thus, 1.0 µg. of the antibiotic agent is equivalent to 1.0 streptomycin unit. The weight recorded on a vial of streptomycin for clinical use does not represent the actual weight of the material contained in the vial but the weight of the free streptomycin base contained in the contents of the vial. An Esch. coli or S unit of streptomycin is that quantity of streptomycin which when dissolved in 1.0 cc. of nutrient broth or agar will just suffice to inhibit the growth of a given strain of *Escherichia coli* (82)

In contrast to penicillin, streptomycin is remarkably stable, both chemically and bacteriologically Solid preparations may be stored in a refrigerator for many months without appreciable loss of activity Aqueous solutions of streptomycin kept at room temperature lose 20 per cent of their potency in 30 days.

Streptomycin, so far as is known, is not destroyed by micro-organisms or the products of micro-organisms Its action is both bacteriostatic and bactericidal, depending upon the concentration of the antibiotic agent. Little is known regarding its mode of action on bacteria. The activity of streptomycin increases as the alkalinity of the body fluid or cultural medium increases (within the physiological range) Thus in infections such as those of the urinary tract, where the urine can be alkalinized the activity of streptomycin is enhanced.

CHEMISTRY

The chemical structure of streptomycin is as yet unknown. The empiric formula is $C_{21}H_{39}N_7O_{12}$ and it contains three basic functional groups—streptidine, *N* methylglucosamine, and a six-carbon, nitrogen free hexose. The disaccharide formed by the union of the two last mentioned compounds has been designated as streptobiosamine

SENSITIVITY OF BACTERIA TO STREPTOMYCIN

The effect of streptomycin on a number of organisms *in vitro* is shown in Table II The sensitivity of a given organism to streptomycin *in vitro* is usually expressed as the minimal amount of streptomycin in micrograms per milliliter of culture medium required to inhibit the growth of that organism. It should be emphasized that organisms vary considerably in their sensitivity to streptomycin, not only from one genus or species to another but from strain to strain. The pathogenic fungi are not sensitive to the action of streptomycin. Pulaski (69) has noted that the effectiveness of streptomycin against streptococci *in vivo* was reduced 4 to 8 times by the presence of 3 per cent blood 10 per cent serum, or 10 per cent plasma. The presence *of blood serum or plasma did not reduce the effectiveness* of the drug against gram negative or gram-positive bacilli. Streptococcic and staphylococcic infections rarely respond to clinical treatment *if the infecting organisms have a sensitivity greater than 8 µg.* of streptomycin per cubic centimeter of culture media (41 69) 76 per cent of penicillin resistant staphylococci and 69 per cent of penicillin resistant streptococci are sensitive to the action of *streptomy*cin (69) Certain organisms notably Eberthella typhosa, are sensitive *in vitro* but infections with these organisms cannot be controlled clinically Why the E. typhosa organisms should be relatively sensitive to the action of streptomycin *in vitro* yet cannot be destroyed in the body when high concentrations of streptomycin in the body fluids are attained is not understood.

It has been repeatedly demonstrated that bacterial organisms which naturally have little resistance to streptomycin can develop a marked resistance *in vitro* by transferring a given organism successively to media containing increasingly larger amounts of streptomycin Increases in resistance of many thousand times has been pro-

TABLE II

Sensitivity of Organisms to Streptomycin

Organism	Sensitivity range, µg. streptomycin/cc. medium
Gram-Negative Bacteria	
Aerobacter aerogenes	0.5 – 64.0
Brucella abortus	0.5 – 3.75
Brucella melitensis	0.5
Br suis	0.5
Eberthella typhosa	1.0 –120.0
Erysipelothrix muriseptica	2.5
Escherichia coli	0.3 – 7.5
Hemophilus influenzae (Pfeiffer's bacillus)	1.88 – 6.0
H. parainfluenzae	30.0
Hemophilus pertussis	1.25 –240.0
Klebsiella pneumoniae (Friedländer's bacillus)	0.6 –256.0
Neisseria gonorrhoeae (gonococcus)	5.0 – 15.0
N intracellularis (meningococcus)	2.0 – 7.5
Pasteurella pestis	0.75 – 1.5
Past. tularensis	0.15 – 2.0
Proteus vulgaris	0.4 – 5.0
Pseudomonas aeruginosa (Bacillus pyocyaneus)	1.0 –400.0
Salmonella aertrycke	4.0 – 30.0
S. enteritidis (Gärtner's bacillus)	4.0 – 30.0
Salmonella paratyphi	3.0 – 30.0
S schottmülleri	2.0 – 30.0
(one strain)	120.0
Salmonella typhimurium	15.0 – 23.0
Shigella paradysenteriae	0.25 – 7.5
Vibrio comma (V cholerae asiaticae)	6.0 – 37.5
Vibrio metchnikovii	7.5
Gram-Positive Bacteria	
Actinomyces bovis	3.75
Bacillus anthracis	0.375
B. mycoides	3.0 – 3.75
B subtilis	1.0 – 7.5
Clostridium butyricum	8.0
Cl. septicum	105.0
Cl. tetani	104.0
Cl. welchii (gas bacillus)	104.0
Corynebacterium diphtheriae	0.375 – 3.75
C. equi	3.75
C. ovis	3.0 – 15.0
C pseudodiphtheriae (Hoffman's bacillus)	3.75 – 7.5
Diplococcus pneumoniae (pneumococcus)	8.0 – 60.0
Mycobacterium tuberculosis	0.15 –300.0
Staphylococcus albus	1.0 – 5.0
Staph. aureus	0.5 –120.0
Streptococcus faecalis	50.0 –100.0
Str equi	2.0 – 15.0
Str haemolyticus	1.0 –120.0
Str lactis	4.0 – 30.0
Str salivarius	5.0 – 25.0
Str viridans	15.0 –120.0

duced in this manner Organisms which become resistant to streptomycin do not show any biochemical or morphologic changes, except in the case of staphylococci in which the pigment production or the fermentation rate of carbohydrates is slightly altered No relationship has been observed between the sensitivity of bacteria and their response to other antibacterial agents. Cultures which have become resistant to streptomycin manifest the same degree of sensitivity to penicillin and the sulfonamides as they did before their exposure to streptomycin (32) The fact that the resistance of a given organism to streptomycin may be increased *in vitro* does not necessarily mean that the resistance to streptomycin will increase *in vivo* Organisms which are easily made resistant may retain their sensitivity in patients, although the patient may have received repeated courses of streptomycin (36)

Therapy with a small amount of streptomycin should not be begun, with the intention of increasing the dosage if a satisfactory response is not obtained. Ideally, the resistance of the infecting organism should be determined before starting therapy, if the organism is moderately sensitive, the initial dose should be an adequate one. Increasing the dose in an effort to eradicate resistant bacteria, or organisms which are becoming resistant, is a practice without rational basis.

DETERMINATION OF SENSITIVITY

The best method of testing sensitivity appears to be the serial dilution method (36 69,78) In this method two series of test tubes are used containing increasing amounts of streptomycin in a neutral medium suitable for the growth of the organism to be tested. One series of tubes is inoculated with the test organisms, the second series with a standard organism of known sensitivity Other methods include the cup–plate method, and agar plates which contain various concentrations of streptomycin (65)

A simple method giving less accurate results consists of placing a disc of blotting paper which has previously been dipped in a solution containing 20 μg. of streptomycin per cubic centimeter on a plate of nutrient agar From the edges of this disc the test organism and a control organism are streaked radially outward. The distance from the disc at which growth appears is a rough measure of the sensitivity of the organism. Tests of sensitivity should be carried out

in media containing no fermentable sugar and in the presence of a pH adjusted close to neutrality, and under aerobic conditions.

ADMINISTRATION

Streptomycin is administered subcutaneously intramuscularly, intrathecally topically orally, and by nebulization. Intravenous administration is not recommended Following intramuscular or subcutaneous administration of ordinary doses, adequate blood levels are maintained for approximately 4 hours. The most widely used method of administration is intermittent intramuscular injection every 3 or 4 hours although intermittent subcutaneous and continuous subcutaneous injections have been used. When intermittent injections are used the streptomycin may be dissolved in 0.5 per cent procaine to alleviate pain.

Although streptomycin is occasionally found in the cerebrospinal fluid in patients with cerebrospinal infections following systemic streptomycin therapy the only reliable method for obtaining a significant concentration of streptomycin in the cerebrospinal fluid is by intrathecal injection. Intrathecal administration should be used in combination with systemic treatment.

The drug has been administered locally in the treatment of infected wounds and burns. The oral route of administration is used to control bacteria within the intestinal tract. Little, if any streptomycin is absorbed from the gastrointestinal tract, so that, if there is evidence of systemic as well as intestinal infection the parenteral, as well as the oral route of administration should be used. Nebulization of streptomycin has been used for treatment of infections of the respiratory tract.

DOSAGE

The usual adult dose for parenteral administration varies between 0.5 and 3 Gm. per day depending on the type of infection being treated. Dosages of 4 to 5 Gm. can usually be tolerated for a few days in special circumstances. The customary dosages are discussed under the different types of infection.

When intermittent injections are used 1.0 Gm. of streptomycin is dissolved in 4.0 cc. of sterile water Use of 0.5 per cent procaine solution as the diluent to reduce the pain of injection will not reduce the potency of the streptomycin.

When used intrathecally in children doses of 25.0 to 30 0 mg. dissolved in 5.0 to 10.0 cc. of sterile physiologic saline solution every 24 hours are recommended. The streptomycin solution is injected after the withdrawal of 5 0 to 10 0 cc of cerebrospinal fluid. For the average adult, 50 0 to 100.0 mg. dissolved in 5 0 to 10 0 cc. of sterile saline solution, can be injected intrathecally For topical administration in the treatment of infected wounds and burns, aqueous solutions containing from 200 to 1,000 μg. of streptomycin per cubic centimeter of solution have been used (40,51) An ointment of carbowax and propylene glycol containing 2,500 μg. of streptomycin per cubic centimeter of ointment has apparently been well tolerated by tissues (51) It would appear that solutions of 100 000 μg. per cubic centimeter are well tolerated in the peritoneal and pleural cavities

A total daily dose of 1 0 Gm. of streptomycin given in three divided doses one with each meal results in concentrations of from 1,300 to 13,000 μg of streptomycin per gram of feces and will produce a marked reduction in intestinal bacteria. From 95 to 98 per cent of the ingested dose is recovered in the feces Streptomycin can be administered orally in any liquid such as milk or fruit juice. It is not appreciably affected by the acidity or alkalinity of food or the intestinal juices. The alkalinity of the feces would tend to enhance the antibacterial activity of the streptomycin. For infections of the respiratory tract, such as tuberculosis of the hypopharynx, larynx, and tracheobronchial tree, 500 μg. of streptomycin are dissolved in 20 cc. of physiologic saline solution and the patient nebulizes and inhales 2.0 cc of this solution every hour for 10 hours a day (39)

DISTRIBUTION

Streptomycin administered in intermittent intramuscular injections every 3 to 4 hours is rather widely distributed in body fluids. (Fig. 5) Administration at the rate of 1.0 Gm per day results in streptomycin concentrations usually varying between 10 0 and 20.0 μg. per cubic centimeter of blood and following a total daily dose of 2.4 Gm., the concentration varies from 12 0 to 35.0 μg. with an average of 16 0 μg. per cubic centimeter of blood The concentration of streptomycin found in pleural and ascitic fluids is approximately

identical with that found in the blood several hours after administration is begun. In the bile of patients with normal liver function the concentration is approximately one-half of that in the blood

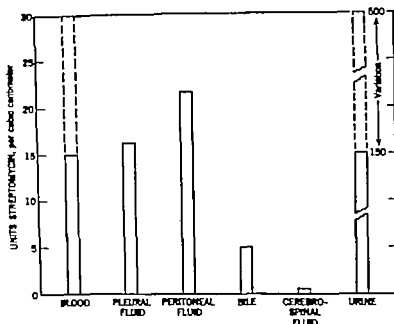


Fig. 5. Distribution of streptomycin in various body fluids following intramuscular injection of 125,000 units every 3 hours for 24 hours. Broken lines indicate variations (90)

in the presence of liver damage the concentration is likely to be reduced (88) Only occasionally are traces of streptomycin found in the intestinal contents

The concentration in the urine following administration at the rate of 1 0 Gm. per day varies between 150 and 500 µg. per cubic centi meter of urine Higher urinary concentrations can be obtained by restricting fluid intake to 2,500 cc per day (68) In the presence of poor renal function, the urinary concentration of streptomycin may be as low as 30.0 to 40 0 µg per cubic centimeter Under these conditions of failure of excretion, the streptomycin may accumulate in the body to such an extent that toxic effects are noted. Pulaski (69) reports the finding of significant amounts of streptomycin in the kid

ney, liver, muscle, and thyroid traces in the prostate and pancreas, and none in lymph nodes, spleen, testes, brain, lung, prostatic fluid, and thick walled soft tissue abscesses following the systemic administration of adequate amounts of the antibiotic

DETERMINATION OF STREPTOMYCIN CONCENTRATION IN BODY FLUIDS

The most accurate method of determining streptomycin concentrations in body fluids is to add varying amounts of the fluid to a series of test tubes containing a liquid medium and a test organism of known streptomycin sensitivity (10,18,67) For most purposes, the cup–plate method of Stebbins and Robinson (78) is satisfactory (36) In this method, various dilutions of the fluid to be tested are placed in cups which have been placed on the surface of an agar plate seeded with a strain of Staph. aureus. The width of the zones of growth inhibition of the organism around the cups is a measure of the concentration of the streptomycin in the cups.

TOXICITY

Streptomycin is referred to in Cushny's Pharmacology (14) as an agent of very low toxicity Although it is capable of producing eighth nerve damage usually no serious reactions are produced unless large doses are used over periods of several weeks. McDermott (55) has emphasized that evaluation of the toxicity of any chemotherapeutic agent must be considered in relation to the disease. The relative dangers of the agent and the relative dangers of the disease should be considered before large doses are employed, or before relatively large doses are continued over long periods

Toxic reactions to streptomycin are of four general types (*1*) irritation at the site of injection and on intrathecal administration (*2*) various manifestations of anaphylaxis (*3*) evidences of renal irritation and (*4*) neurologic disturbances. We have not encountered the "histamine" type reaction since methods of manufacture have been improved. In regard to local irritation, the injection of highly purified streptomycin causes no more local irritation than does highly purified penicillin (55) There appears to be no difference between the local irritation caused by the hydrochloride or the sulfate salts of streptomycin. Following intrathecal administration of 0.05 to 0.1

normal patients (90) In dogs and monkeys a reversible fatty infiltration of the liver and kidneys has been found.

USE OF STREPTOMYCIN

In Urinary Tract Infections

Streptomycin is useful in the treatment of urinary tract infections, especially in many infections resistant to sulfonamide and penicillin therapy such as infections caused by Esch. coli, Proteus vulgaris, Aerobacter aerogenes Pseudomonas aeruginosa, and the nonhemolytic streptococci (51) Helmholz (33), on the basis of *in vitro* studies, expressed the opinion that streptomycin was the most potent urinary tract antiseptic available. Keefer (47) reports that of 409 patients with urinary tract infections, most of which had previously been treated with penicillin and sulfonamides, 42 per cent recovered and an additional 35 per cent were improved. At the Hospital of the University of Pennsylvania a number of patients most of whom had renal disorders in addition to urinary tract infections, were treated with streptomycin. Almost all had infections which were resistant to the usual types of urinary tract antiseptics. The associated urinary tract pathology included diverticuli calculi rectovesical fistulas, congenital anomalies cystostomies ureterostomies nephrostomies and carcinoma. Streptomycin produced recovery either symptomatic or bacteriologic or both in 60 per cent of these cases. The 6 patients who did not have associated urinary tract pathology recovered completely and have not had recurrences of the infection. The recurrence rate was high in the patients who did have associated urinary tract pathology While many patients will not be cured by streptomycin, they can be temporarily improved and made more suitable candidates for operative procedures if such are indicated. Good results with streptomycin in urinary tract infections associated with other types of urinary tract pathology can be expected only when proper urologic treatment is undertaken before or in conjunction with streptomycin therapy It is unreasonable to expect the infection to be cured by any urinary tract antiseptic, as long as the contributory cause of the infection has not been abolished.

Approximately 20 per cent of all patients with infections of the urinary tract will show an initial response to streptomycin therapy but will relapse during therapy There are relapses in another 20

per cent shortly after therapy is discontinued, especially in those with associated urinary tract pathology Patients with the most marked constitutional symptoms usually respond dramatically to streptomycin, while those with mild symptoms respond irregularly (38)

For the treatment of urinary tract infections 2 4 to 3.0 Gm of streptomycin per day for 3 days is usually sufficient (68) Prolongation of therapy seldom causes improvement. Urinary concentration of streptomycin with the above doses usually varies between 500 and 2 000 µg. of streptomycin per cubic centimeter of urine. Higher

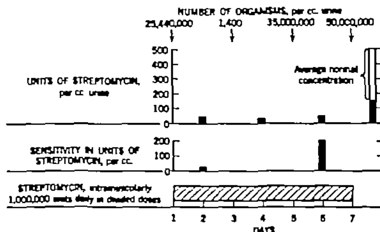


Fig 6 Effect of decreased renal function on streptomycin therapy of urinary tract infection with Bacillus pyocyaneus (9?)

concentrations are obtained by restricting the fluid
cc. or less per day Patients with low renal function
low urinary concentrations of streptomycin (Fig. 6
that therapy may be ineffective. High blood
streptomycin is retained in the body
possibility of severe toxicity is great.

Helmholz (33) has pointed out the
urine since the activity of streptomycin
medium (Table III) Gilligan et al.
12.0 to 15.0 Gm. of sodium bicarbonate
be reasonably certain of an alkaline
of patients an initial dose of 4.1

by 2.0 Gm. of sodium bicarbonate every 4 hours during streptomycin therapy apparently produces a satisfactory reaction in the majority of patients. In 64 cases treated by Hewitt (38) with streptomycin alone, bacteriuria ceased in 20 per cent, whereas in 11 patients treated with streptomycin and alkali bacteriuria ceased in

TABLE III

Amount of Streptomycin Required for 50 per cent Inhibition of Escherichia coli at Various pH Levels (23)

pH 5.0	2.0 units per cc.
pH 6.0	1.0 units per cc.
pH 7.0	0.3 units per cc.

75 per cent. In serious infections there are no contraindications to combined antibiotic treatment, such as the use of streptomycin and penicillin. Local irrigation of the urinary tract with solutions of streptomycin has not been beneficial in the few patients treated in this manner (68) When streptomycin first became available a small number of encouraging results were obtained in tuberculous urinary tract infections but the late results have not been good While the initial response is quite often encouraging, most of the patients sooner or later show signs of active infection Surgery is the method of choice in the treatment of unilateral tuberculosis of the kidney Streptomycin should, however be used in the immediate preoperative and postoperative periods.

In Peritonitis

Although penicillin and the sulfonamides have been very useful in the treatment of peritonitis, even in conjunction with adequate surgery and adequate supportive therapy these agents often fail to control peritoneal infection. The availability of an agent active against gram negative bacteria and with some activity against gram positive bacteria led to speculation as to its usefulness in the treatment of peritonitis. Keefer (47) reported 53 patients with peritonitis treated with streptomycin. Among the 53 patients there were 12 deaths He points out that there were but 3 deaths in 21 patients with peritonitis following appendicitis. The dosage used ranged between 1.0 and 2.0 Gm. per day for 8 to 10 days. Keefer concluded that the results are sufficiently encouraging for strepto-

mycin to be used in all cases of peritonitis in which the infecting organism is a susceptible one.

In an attempt to demonstrate the usefulness of streptomycin in the treatment of peritonitis Murphy *et al* (59a) tested the effectiveness of streptomycin in the treatment of experimental peritonitis in the dog. They first demonstrated that streptomycin administered intramuscularly diffused into the normal peritoneal cavity and into the peritoneal exudate of peritonitis After a lag of about 2 hours following each injection, the concentration of streptomycin found in the purulent peritoneal exudate was roughly equivalent to the concentration found in the blood when the streptomycin was administered by intramuscular injections every 4 hours. The survival rate of the animals with experimental peritonitis treated with streptomycin was 70 per cent, as compared to the survival rate of 30 per cent in the untreated animals Fauley *et al.* (22) using penicillin found a survival rate of 41.7 per cent (if the animals which developed fistulas and pneumonia are not excluded) as compared to a control survival rate of 7 4 per cent. Although the Fauley modification of Bower's (7) technic was used by both groups of investigators, the results cannot be compared directly because of the discrepancies in the survival rate of the control animals observed by the two groups of investigators, e.g. 30 per cent by Murphy *et al* and 7 4 per cent by Fauley *et al* Epps Levy and Howard (21) found that sulfanilamide or sulfathiazole produced a survival rate of 50 per cent as compared to a control survival rate of 8.3 per cent. Thus, penicillin, the sulfonamides and streptomycin have produced survival rates 34 to 43 per cent greater than was observed in the respective control groups.

Since the sulfonamides, penicillin, and streptomycin have different ranges of antibacterial activity and since peritonitis is in the majority of instances a mixed infection of gram positive and gram-negative organisms it seems reasonable to expect a greater effect from the use of two or more of these agents Various combinations were tested to determine the effectiveness in the treatment of experimental peritonitis. For the experiments a more virulent type of peritonitis was produced than that produced by the method of Bower (45) Streptomycin alone was not as effective as a combination of penicillin and sulfonamides. However when streptomycin was added to the combined penicillin and sulfonamide therapy an even

greater percentage of animals survived Finally, it was shown that a combination of penicillin and streptomycin was just as effective as these two agents plus local and systemic sulfonamides Thus, the combined penicillin and streptomycin therapy was as effective or more effective than any of the other combinations used (89) A number of patients with peritonitis have been treated at the Hospital of the University of Pennsylvania with 2 0 Gm. of streptomycin and 1 000 000 units of penicillin daily with very gratifying results.

Although one is reluctant to recommend multiple therapy, it would appear under the circumstances that such therapy is to be recommended for a mixed infection of several types of gram-negative and gram positive bacteria. Often it is impossible to know the quantitative bacteriology of peritonitis and therefore impossible to know whether the invading organisms would respond better to one agent than to another Furthermore, Carpenter *et al* (11) have *shown that the ability of an organism to develop resistance in vitro* is nearly abolished when several antibacterial agents are used simultaneously

In Prophylaxis in Surgery of Large Bowel

Oral streptomycin is effective in reducing the bacterial flora of the intestinal tract (71a) By reducing the number of bacteria in the feces, the amount of bacterial contamination of the peritoneal surfaces can be reduced in elective surgery of the large bowel regardless of whether a so-called "aseptic technic" or an open technic is used.

In a series of 27 patients *15 were treated with a total daily dose* of 1 0 Gm. of streptomycin and the remaining 12 patients were treated with sulfasuxidine (succinylsulfathiazole) 0.25 Gm. per kilogram of body weight per day These patients did not have clinical signs of intestinal obstruction and they did not receive enemas or laxatives during the period of observation. A low residue diet was used. Tables IV to VI (page 257) and Figures 7 and 8 (page 258) show the relative effectiveness of the two agents Quantitative and qualitative bacteriologic studies were made before and every second day during therapy It was found that streptomycin was much more effective than sulfasuxidine in the *dosages administered not only* in reducing the relative number of Bacillus coli, but also the Strep faecalis and the clostridial organisms in the feces. From the results of these studies, it appears that 8 days are required both with sulfasuxidine

and streptomycin, if a maximum effect is to be achieved against the clostridial organisms. When streptomycin or any other agent which reduces the number of bacteria in the gastrointestinal tract is used, vitamin K should probably be administered to prevent hypoprothrombinemia (61)

TABLE IV

Effect of Streptomycin and Succinylsulfathiazole on the Number of Escherichia coli per Gram of Feces

Agent	Before administration	After 8 days	After 8 days in 85 per cent of patients
Streptomycin	74,826,060,000	418,000	262
Succinylsulfathiazole	23,700,000,000	150,000,000	98,857

TABLE V

Effect of Streptomycin and Succinylsulfathiazole on the Number of Streptococcus faecalis per Gram of Feces

Agent	Before administration	After 8 days	After 8 days in 85 per cent of patients
Streptomycin	900,500,000	77,200	0
Succinylsulfathiazole	769,000,000	174,500,000	141,157,833

TABLE VI

Effect of Streptomycin and Succinylsulfathiazole on the Number of Clostridia per Gram of Feces

Agent	Before administration	After 8 days	After 8 days in 85 per cent of patients
Streptomycin	33,030,000	539,900	200
Succinylsulfathiazole	15,000,000	1,047,000	71,218

In a limited number of patients prepared for operation with streptomycin by mouth and treated postoperatively with a combination of streptomycin and penicillin parenterally the postoperative course has been uncomplicated. Figure 9 shows the postoperative course of a patient with a carcinoma of the sigmoid colon who had primary resection and anastomosis

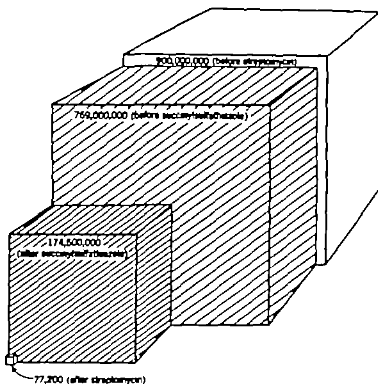


Fig. 7 Relative effect of streptomycin and succinylsulfathiazole on the number of Streptococcus faecalis per gram of feces (71a)

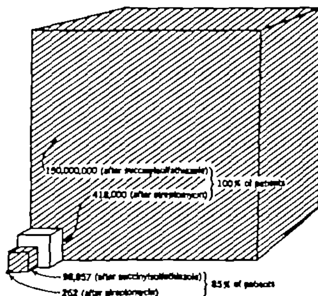


Fig. 8. Relative effect of streptomycin and succinylsulfathiazole on the number of Escherichia coli per gram of feces (71a)

Primary resection sigmoid colon

Out of bed

Discharged

Organisms per gram of feces

445,200,000 4,232,000 230 0 — B. coli

3,160,000 3,000 100 0 — Strep. faecalis

18,160 78,000 60,200 51,200 — Clostridia

STREPTOMYCIN 1,000,000 units by mouth in 4 divided doses daily

PREOPERATIVE DAYS

POSTOPERATIVE DAYS

Fig. 9 Effect of streptomycin in primary resection of the left colon (88a)

In Cholangitis

Recurrent infection of the biliary tract in the presence of partial common duct obstruction or in the absence of a functioning sphincter of Oddi, has always been difficult to treat adequately When 1.0 Gm. of streptomycin per day was administered in divided doses every 3 hours to patients without liver damage, the concentration of streptomycin in the bile varied between 7.0 and 12.0 µg. per cubic centimeter of bile. It seems likely that streptomycin might be an effective form of therapy early in the course of a recurrent cholangitis Recurrent cholangitis with the inevitable liver damage which results presumably would not respond to streptomycin therapy because the severely damaged liver *is unable* to *excrete* appreciable amounts of streptomycin in the bile (88)

In Osteomyelitis

Since the ordinary form of hematogenous osteomyelitis is due to hemolytic Staph. aureus infection, the drug of choice in the treatment of this disease is penicillin. However, the hemolytic Staph. aureus organisms may be penicillin-resistant, and occasionally, other causative organisms will be found. *When these* organisms are penicillin resistant and streptomycin-sensitive *streptomycin should* obviously be used Keefer *et al.* (47) have reported good results with streptomycin in the treatment of osteomyelitis in a few cases in which the causative organisms were streptomycin-sensitive. A case

of typhoid osteomyelitis, in which streptomycin was used as an adjuvant to surgery has been reported by Royster *et al.* (78)

In Septicemia

Streptomycin treatment of septicemia and bacteremia due to the general group of gram negative bacilli has been very gratifying. When due to Esch coli Ps aeruginosa, P vulgaris A aerogenes, K. pneumoniae and H. influenzae the infections usually respond well to this type of therapy It should be remembered that occasional strains of streptococci, staphylococci and other organisms which usually respond to sulfonamide and penicillin therapy may actually be resistant to these agents. This fact is another reminder that the intelligent use of the antibiotics and chemotherapeutic agents calls for determination of the sensitivity of the infecting organism. Futhermore the source of the blood stream infection must be eradicated regardless of the chemotherapeutic or antibiotic agent used. If there is a localized purulent collection from which organisms gain entrance to the circulating blood it must usually be abolished by surgical means in order to ensure against recurrence of the septicemia. Streptomycin administered systemically will not sterilize walled off collections of purulent material, even though the infecting organism is sensitive to the action of the drug (47)

In Tularemia

The effect of streptomycin in the treatment of tularemic infections is unquestioned. Indeed it is considered a specific in this condition. It can be stated that streptomycin is extremely effective in the treatment of tularemia and that it is much more effective than any other type of therapy (22) Adequate dosages for cases of the usual severity with or without tularemic pneumonia, are either 0.5 Gm. per day for 2 days followed by 0.25 Gm. per day for 4 days, or 0.5 Gm. per day for 6 days (22) Foshay suggests that in the presence of septicemia up to 4.0 Gm. daily be given for 7 days or longer

In Tuberculosis

Streptomycin is the most effective agent yet known for the treatment of tuberculosis However the results have been somewhat disappointing in the treatment of tuberculosis of the genitourinary tract. Marked temporary improvement occurs in 50 per cent of the cases, it will therefore probably be useful in preoperative and post

operative treatment. It should not be used as a substitute for surgery in cases of unilateral renal tuberculosis. The drug is also used before and after thoracic surgery for pulmonary tuberculosis. Streptomycin is not a substitute for the established methods of treating tuberculous infections such as adequate nutrition and rest. The tuberculous infections which have responded to therapy include the pulmonary, miliary and tracheobronchial forms of tuberculosis, as well as tuberculous meningitis tuberculous empyema, and tuberculous sinuses of soft tissues In regard to tuberculosis of the tracheobronchial tree it has not been determined if either nebulization or systemic therapy alone would suffice. Old, established tubercular infections of the fibrocaseous type do not respond to streptomycin therapy Because of the toxicity of streptomycin, tuberculous lesions in which one would expect a satisfactory response to ordinary therapy probably should not be treated with streptomycin.

In Wounds

Preliminary reports indicate that streptomycin is useful in the treatment of contaminated and infected wounds. However one must be cautious in evaluating any type of local wound therapy The earlier reports on the use of the sulfonamides and penicillin in wounds were also encouraging, but it is now becoming fairly certain that the sulfonamides and penicillin do not cure established localized mixed wound infections. Penicillin is inhibited by the powerful penicillinase elaborated by gram-negative bacilli (56) The sulfonamides and penicillin diffuse poorly into fibrin (62)

We have found that streptomycin applied locally in high concentrations is effective in the treatment of experimental wounds contaminated with gram positive and gram negative organisms (51) In the control group of animals, 91 per cent of the wounds were infected on the tenth postoperative day whereas in the animals which received 50,000 µg. of streptomycin in 10.0 cc of a mixture of propylene glycol and carbowax locally the wounds were infected in only 30 per cent of the animals When this therapy was delayed 8 hours after traumatization of the tissue and contamination with a mixed bacterial culture the results were as good as when the streptomycin ointment was applied immediately after production of the wound. In a fourth group of animals systemically administered streptomycin appeared to protect the animals to an equal extent.

from the earliest times there is a surprising dearth of records prior to 1940 One reason is that in the earlier literature the condition was confused with frostbite but Critchley (25) from accounts of shipwreck ranging from the sinking of the *Luxborough Galley* in 1727 up to the loss of the *Titanic* in 1912 was able to trace a few reports of cases which may well have been immersion foot Another reason is that in peacetime shipwrecks occur near land on recognized sea routes or at fishing grounds where there are usually several boats in company so that survivors are quickly rescued Minor degrees of immersion foot may occur in fishermen who have worked in bitter weather knee deep in water and fish

Descriptions of trench foot as it occurred in the First World War (24 45,85) the Spanish Civil War (38 62 67) and World War II (1 6 17,29,31,32 68 74) present a clinical picture similar to that of immersion foot. Discussion with experienced observers of trench foot in Europe and America, and a study of their cases have strengthened my belief that the two conditions are akin if not identical

The first case I saw was in February 1940 that of a boy aged 17 serving on a destroyer in the North Sea During six days of cold, rough weather he suffered from seasickness He wore rubber sea boots continuously not even removing them at night On the sixth day he noticed that the boots had become tight. When he kicked them off the feet felt numb and itched and were so swollen that he was unable to get the boots on again He hobbled painfully to the sick bay, where he was seen by a medical officer

When a pair of socks and two pairs of sea boot stockings were removed the feet were damp probably from condensed perspiration. The feet and lower third of the legs were very cold to the touch, and remained so even after attempts at warming The toes were dark blue, the dorsum and soles purplish red Edema was relatively slight. *In the feet and ankles he was unable to appreciate the pain* of pinprick or the heat of a hot test tube yet the feet were hypersensitive to the pressure of bed clothes and the putting on of socks. He complained of numbness and tingling and of much pain. Pain grew worse as the feet were warmed by hot bottles and these were soon removed

By the time he reached hospital several hours later the feet had become hot and of a mottled bluish red color Swelling which pitted on pressure had greatly increased and extended to the lower third of the legs There was a small ecchymosis beneath the right great

toe Even light pressure on the soles was painful and he was unable to stand. For several nights he could not sleep because of aching in his feet.

When I first saw him 4 days after the onset of symptoms his feet were hot, swollen, and pink, with a slight bluish tinge. He was almost completely unable to move the toes He could not detect light touch over the distal parts of the soles of the feet and the under surface of the toes nor discriminate between the sharp and blunt ends of a pin But these parts of the feet were extremely hyperesthetic to pressure stroking, or light handling.

Five days after coming into hospital with no treatment except rest in bed edema had completely disappeared Power improved and at the end of 10 days movement of the toes was almost complete The area of sensory disturbance shrank toward the periphery In $3^1/_2$ weeks hyperesthesia had disappeared and the heat and redness had largely subsided. After 6 weeks sensory loss was confined to the inner aspects of the ends of the great toes (Fig 1)

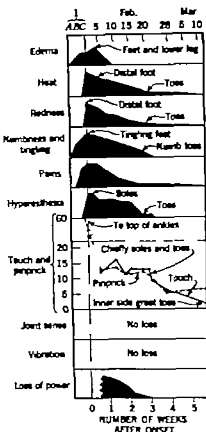


Fig. 1 Rate of recovery in patient TR2 who had mild immersion foot (grade B1) For sensory tests the extremities were divided into numerous small areas the total number of insensitive areas was charted, partial loss counting as /₂. To indicate the course of events on February 1, this day has been allotted a larger space, and subdivided into sections A B and C.

The term "immersion foot had not then been invented and the case was written up as "trench foot in a sailor It was not until several months later that patients arrived with the label "immersion foot," a term coined by Surgeon Captain D Arcy R.N., to describe the injury sustained by survivors from H.M.S *Glorious* an aircraft carrier sunk in June 1940 by shellfire off Narvik. This port is on the northwest tip of Norway within the Arctic Circle. Sea and air

temperatures were probably in the region of 8 3 C * Of the ship's company of 1,500 officers and men about 400 reached Carley floats where most of them died within a few hours Hundreds more must have perished in the water before ever reaching the floats





Fig 2 Carley float (above) under practice conditions, and (below) in an actual rescue

These floats are large rectangular structures made of a steel cylinder with an open rope network in the center (Fig 2) For the first 12 to 14 hours the floats were greatly overcrowded (30 or 40 men in a float) and the men stood on the rope network often immersed almost to the waist and with no room to move. By the

* Figures by courtesy of the Royal Naval Meteorological Branch

next day the few men who survived were able to sit on the sides of the float with their feet immersed or even to remove them from the water Some were too weak to move about others exercised a little using a paddle Chilled by immersion even before they reached the floats the men were also underclad—cotton singlet and short pants shirt, and either cloth jacket and trousers or a pullover and overalls Most of them had kicked off their shoes They had neither food nor water When after 2 $^{1}/_{2}$ days the rafts were sighted by a Norwegian trawler only 38 men remained alive 3 died later

In the trawler which carried no medical officer some of the men had their feet warmed rapidly before the galley stove or immersed in warm water These men are said to have had more pain and swelling at the time on the final analysis however it could not be demonstrated that vasoneuropathy in these men was any more severe than those whose feet were not warmed. All of the 35 survivors suffered from peripheral vasoneuropathy after chilling 18 cases were studied in detail and have been followed up at intervals for 6 to 7 years

In a few the grade of immersion foot was mild with reversible nerve lesions in the majority it was moderately severe with degenerative nerve lesions 2 had very severe immersion foot with gangrene In all but 2 cases the hands were also affected although less severely than the feet. Only 3 men had moderately severe immersion hand with a rate of recovery pointing to irreversible nerve lesions

The following case (G7) is typical A petty officer aged 30 had swum for about 15 minutes before he reached a float. At first there were 30 or 40 men in the float and he stood for 2 or 3 hours immersed to the waist, with little room to move Later that night, after 12 men had died he was able to sit on the side with his legs immersed to the knees He had kicked off his sea boots before jumping into the water but was still wearing socks His legs quickly became numb The next morning the sea was calmer and there was more room on the float he was able to sit on the edge with his feet out of the water His feet were still numb and soon his hands felt numb also and became white Although the sun appeared only occasionally his body did not feel very cold. If he shivered he took a deep breath and held it this "stopped the shivering and warmed him up Although thirsty he refrained from drinking sea water or moistening his mouth with it.

He exercised with his arms only he did not have a paddle. By Sunday night, only 3 men were left alive He continued to keep out of the water and quite often lay down and slept for short period On

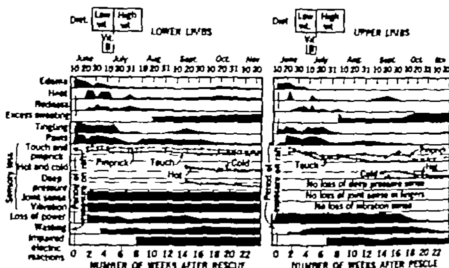


Fig. 3. Progress in patient G" suffering from moderately severe immersion foot and hand (grade C6) (89) Sensory loss was charted as in Figure 1. *Progress was not influenced by administration of thiamine*

Monday morning his body began to feel cold. His hand were numb to the wrist and his legs to below the knees The 3 men were very weak by this time and found it a hard job to lift one body out of the float. On Tuesday morning, when the Norwegian trawler came alongside he could hardly hold the line Unable to walk he was carried to the galley stripped put in dry clothes and given hot drinks His feet, which were very much swollen were dipped for one minute into water which was steaming a little later olive oil was applied. When he left the trawler after 2 days his hands and feet *were still swollen, white and cold (in most cases redness* and heat appeared within a few hours of rescue) He spent 2 days ashore during which blisters on the toes and calves were opened and dressed. On the passage (fourth to seventh day after rescue) his hands ached and he was kept awake by shooting pains in the feet He had difficulty in walking and in cutting up his food

I first saw him 10 days after rescue. He was a well-developed man but rather thin, his weight having fallen from 167 to 150 pounds The

weight lost was soon regained. There were no signs of disease in heart, lungs abdomen optic fundi or cranial nerves. The pulse was 64 per minute blood pressure 122/70 There was no roentgenographic evidence of cardiac enlargement Electrocardiograms showed right axis deviation. Blood counts were normal



Fig 4 Muscle wasting in moderately severe immersion hand in patient G7

Upper Extremities The hands were swollen, pink, and hot Passive movements were limited and he could not make a fist. He was unable to write or use a knife and fork, and needed both hands to lift a cup Not all this disability was due to swelling subsidence of the edema revealed considerable wasting and loss of power in the intrinsic muscles, reminiscent of progressive muscular atrophy (Figs 3 and 4) Electric responses showed the reaction of degeneration.

There was numbness with sensory impairment to touch and pinprick on the palmar surfaces nearly to the wrist and on the dorsum of the distal segments of the digits Joint sense and vibration sense

were somewhat impaired in the fingers Stereognosis was defective he was unable to recognize coins as such and a safety pin was described as "something soft."

Tingling, chiefly in the fingers and palm lasted 8 weeks Aching and occasional shooting pains were present for 14 weeks Slight hyperesthesia, a tingling of the fingers when touched was noted in the third fourth and fifth weeks

After 8 weeks the hands, which until then had shown a variable degree of heat and redness began to sweat excessively and were unduly sensitive to cold In cold air or after washing in cold water the fingers became painful cold and stiff and subsequently painful and red Faradic stimulation of the palms produced pools of sweat particularly beneath the electrode By this time sensory loss had considerably diminished particularly in the palms

Sensation was practically normal at 18 weeks Paralysis and wasting of the intrinsic muscles were unchanged for 17 or 18 weeks and then improved rapidly

Lower Extremities The feet were hot and red, and pulsation could be felt in the dorsal pedal and posterior tibial arteries Pitting edema involving the dorsum of the feet ankles and lower half of the legs lasted about a month There were old blisters on the calves and the dorsum of certain toes which took nearly 6 weeks to heal

Stabbing and aching pains and tingling began within an hour of rescue their onset perhaps accelerated by the warmth applied Pains were at their worst in the first 2 days. Stabbing pains lasted 6 weeks aching and tingling for 11 weeks, but there were recurrences later Superficial hyperesthesia was present, but trivial Later as he walked more there was deep tenderness over the soles The pattern of sensory loss 10 to 14 days after rescue was equivalent to that shown for grade C6 in Figure 15 In the great toes joint sense was grossly defective and vibration sense absent.

He was able to move the toes very little although passive movement was free Intrinsic muscles of the feet, and some distally innervated muscles in the legs showed the reaction of degeneration. Wasting of the feet became evident later

A portion of digital nerve was excised from the lateral aspect of the left great toe 3 months after rescue The biopsy showed Wallerian degeneration of about 90 per cent of the nerve fibers (see ref 13a case 3) Despite the anesthesia, the wound healed by first intention.

Unlike the hands the feet showed little motor or sensory recover at 24 weeks At 8 weeks there was spontaneous excess sweating o the dorsum of the feet At 22 weeks the patient developed a eczematous reaction with vesiculation in this area, ascribed to hyper hidrosis At 15 weeks, body heating evoked sweating over the inne aspect of the sole and on the dorsum of the toes even though thes areas remained insensitive to light touch of cotton, pain of moderat pinprick and even deep pressure" There was, however a well circumscribed area of complete anhidrosis over the lateral aspect o the left great toe—the area supplied by the nerve removed at biops a few weeks before Although all parts of the dorsum of the toe were equally anesthetic this small patch was the only area no supplied with sudomotor fibers Evidently during recovery fron immersion foot, the sweat fibers and their end organs had regaine function sooner than those concerned with touch pain, and dee pressure.

The feet, which for the first few months were habitually warn later became cold-sensitive and were always icy cold."

This was one of a series of cases to receive a high vitamin die with daily supplements of 50 mg. of vitamin B_1 60 Gm of whea germ, 50 mg. nicotinic acid 500 mg. ascorbic acid and large dose of a concentrate of vitamins A and D The regime appeared to hav no effect on the rate of recovery

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The history of the immersion foot syndrome falls naturally int four phases

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however the color is described as pale yellowish white blue or mottled blue and black. Although the predominant feature is vasoconstriction phases of vasodilatation must undoubtedly occur one survivor remarked that during exposure his left foot became temporarily hot and red and afterward cold again Blistering is uncommon during exposure but the sodden skin is friable and serious damage may follow minor injuries

Prehyperemic Stage In this stage there is a direct continuation of the events occurring during exposure In our base hospitals it was difficult to make firsthand observations of the earliest stages after rescue Much useful information was obtained from the medical officers of ships The description of the prehyperemic stage and of the transition to the hyperemic stage is based largely on the findings of Surgeon Lieutenant-Commander G D Channell R.N V R (23) in 26 merchant seamen picked up by a destroyer in the North Atlantic after having been adrift for 10 days with sea temperature between 7 1 and 8.8 C and air temperatures of 8 8 to 12 C Information pertaining to the early stages in more severely damaged limbs proceeding to extensive gangrene was obtained from Dr S Bartlett of the Isle of Barra (4)

For some hours after rescue the feet remain numb and feel heavy Survivors are frequently unable to maintain their balance or if able to walk they describe the sensation as "walking on air " or "walking on cotton wool " Ankle and toe movements are absent or impaired. There is a stocking' type of sensory disturbance varying from hypoesthesia and hypalgesia in mild cases to complete loss of all forms of cutaneous sensation in severe cases. In the early stages it is common for sensory loss to extend as high as the midcalf Joint sense may be lost in the toes and ankles. The chilled portions of the limbs remain cold and are pale or blue—often white with scattered cyanotic areas. Severe cases may show large black, blue-greenish or yellowish patches on the legs Swelling varies with severity of exposure but a tense edema often extends to above the knee. In this stage blistering is still unusual and it is difficult to be certain of areas that will become gangrenous Except in very mild cases, pulsation is absent in the peripheral arteries (posterior tibial and dorsal pedal) and the cutaneous circulation, as tested by blanching with finger pressure is very sluggish.

Hyperemic Stage This follows the prehyperemic stage Within 2 to 5 hours of rescue, the affected parts become hot, red painful more

swollen, and perhaps blistered In severe cases patches of gangrene usually superficial may appear damage to nerves declares itself in anesthesia, and in motor vasomotor and sudomotor paralysis The duration of the hyperemia varies according to the severity of the case from a few hours or days to 14 weeks or more

Posthyperemic Stage Mild cases pass from the phase of warmth to normality In the typical moderately severe case of immersion foot, transition from hyperemia to posthyperemia occurs but it is never abrupt. In this stage inflammation has subsided vascular tone has recovered and skin temperature has fallen. Complete recovery in more severe cases must await regeneration of the peripheral nerves This is often preceded by signs suggesting partial reinnervation of end organs and effector organs—cooling (with a cold-sensitive state) a partial recovery of sensation (with hyperpathia) and of sweating (with marginal hyperhidrosis) Late sequels include recurrence of pain, tingling, swelling, or blisters persistence of a cold-sensitive state or of hyperhidrosis and occasionally circulatory deficiency suggestive of vascular occlusion

According to Professor Orloff of Archangel (64) the after-effects of immersion foot may last for many years and relapses are common. We have seen patients who were considered to have been mildly affected still complaining after 5 or 6 years Many patients remain well while ashore but may have recurrence of symptoms when they return to sea in northern latitudes

Experience gained in earlier work, when brought to bear on later cases in this series led to clarification of certain points hitherto obscure. Case B1 is an example, and will be referred to frequently in the discussion which follows This patient was one of 3 survivors adrift for 34 hours on a raft in the North Sea in January 1943 One man died during exposure pathologic findings have been described elsewhere (ref 12 case 1) When the other 2 men reached hospital a few hours after rescue their feet were cold blue, and moderately swollen. During the night the feet became hot (32 to 34.5 C) and more swollen. With the legs horizontal the feet were slighty red pendent, they became congested to a deeper color with a slight bluish tinge elevated they blanched rapidly Peripheral arteries pulsated strongly Power was deficient in the toes and electric reactions were somewhat impaired in distally innervated muscles Sensory loss to light touch (cotton) and pain (pinprick) was chiefly confined to the plantar surfaces of toes, distal soles and heels lateral

the digits were already warm and within a few hours reached full vasodilatation level (35–36 C.)

When fully developed, the hyperemia is of sock or glove distribution, similar in extent to the coldness and blueness noted on rescue At first the redness is not general Some areas may remain blue in color but feel as hot as the adjacent flushed skin 15 to 24 hours

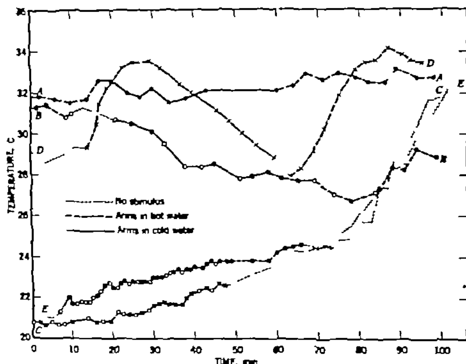


Fig. 6 Vasomotor reactions in left great toe at various stages in moderately severe immersion foot in patient B1 (80) *A* at 9 days toe hot no vasomotor responses (room temp 20–21 C.) *B* at 43 days toe hot but some vasomotor responses (room temp 20–21 C.) *C* at 80 days toe cold vasodilatation delayed and gradual (algid state) (room temp 21 22 C.) *D* at 83 days toe hot but definite vasomotor responses (room temp 21–22 C.) *E* at 130 days now in posthyperemic stage events as in *C* room temp 21.7–22.5 C

after rescue the hyperemia is at its maximum and the limb has a somewhat "beefy" appearance Areas that are threatened with gangrene do not become warm, but the hyperemia is intensified around them, forming a distinct line of demarcation. At this time there is every evidence of an exceedingly active circulation. Within 2 to 8 hours of rescue pulsation returns to the peripheral arteries and rapidly becomes full and bounding.

be no further rise in the skin temperature of the distal parts even after nerve block. During immersion of the arms in hot and then cold water the toes remain hot, a sign that reflex vasomotor activity is impaired or absent (Fig. 6A)

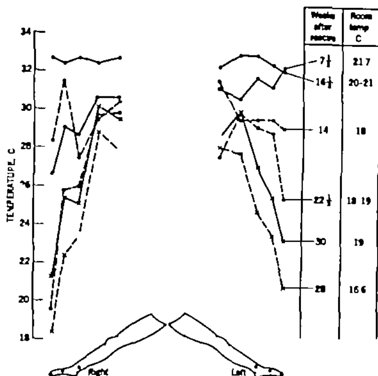


Fig 10 Skin temperature gradients in patient ST6 who had gangrene of the left great toe (90) Even in the right foot where there was no necrosis temperature gradient remained abnormal as late as 16½ weeks after rescue

In several respects these findings are comparable with those after postganglionic sympathectomy and are presumably attributable in part at least to interruption of vasoconstrictor fibers in peripheral nerves but there are other findings such as the color changes on pendency and elevation which cannot be explained on this basis

At a later stage slight cooling of the extremities becomes apparent, but there is still evidence of diminished vasoconstrictor tone in the feet so that the toes remain warmer than normal Reflex vasomotor activity may now be demonstrated in the toes but the response is gradual (Fig 6B)

The duration of the hyperemic stage varies from a few days to a few months depending on the severity of the injury It is possible that even the mildest cases have a transient hyperemia which passes unnoticed In cases of moderate severity, the hyperemia lasts from 6 to 10 weeks. Toward the end of this period, the hyperemia begins to show signs of instability and the affected extremities may on occasion be found to be cool or cold



Fig. 11. Gangrene of great toe in patient ST6, 9 days after rescue (90) Immersion foot was not otherwise very severe (right, grade B3 left, grade B4) Gangrene was partly attributable to heat applied in the prehyperemic stage

In the posthyperemic stage when a normal vasoconstrictor gradient has been restored and the feet are almost habitually cool many degrees of reflex vasomotor activity may be observed. Mild cases may show normal vasomotor reactions within a few weeks of rescue Other cases may show a conspicuous delay before normal vasodilatation occurs (Fig 7 left great toe) Occasionally, there is complete failure of reflex vasodilatation. These findings are related to the development of sensitivity to cold This state which may last for many years merits special consideration.

COLD-SENSITIVE STATES

Sooner or later more than half of our patients with immersion foot complained that their limbs were sensitive to cold, that is, that they cooled to an abnormal degree and took hours to warm up In the hands particularly attacks of Raynaud's phenomenon were fre-

quent. Even in patients who have been followed up for as long as 6 years the symptoms of cold-sensitivity have usually persisted. A notable exception is case *RF1* in which peripheral vasoneuropathy affecting the left hand was followed by a cold-sensitive state which passed off completely in a few months and caused no further trouble even during high altitude flights at temperatures as low as —35 C

Evidence of cold sensitivity may appear during the transition from *the hyperemic to the posthyperemic stage.* On some days the feet, previously consistently warm are noted to be cool (Fig. 5) At first there is always some precipitating factor which causes the feet to become cool (e g a tepid bath walking barefoot on a cold floor etc) but later the feet become cold spontaneously Once cold they *tend to remain cold for several hours and even when means of* rapid warming are applied such as immersion of arms in hot water warmth to trunk and thighs, or hot drinks they regain their previously warm state very gradually (Fig 7 left great toe) The cold distal parts of the extremities are sharply demarcated The lower limits of warmth gradually *proceed distally* Once the skin temperature of the toes rises above a certain critical level e g. 24 C warming proceeds more rapidly indicating that relaxation of vessels has occurred (Fig. 7, left great toe) This delayed warming up phenomenon is part of the algid state a state induced whenever the skin temperature falls below a certain level.

Interesting observations have been obtained by recording skin temperatures during periods of cooling by means of a fan (86) In case B1 at 17 days *it was shown that even after prolonged cooling* to a low level (17 C) the feet warmed up spontaneously but at a slow rate which indicated that vasoconstriction had been induced (Fig. 8) Less severe and prolonged cooling was followed by a fairly rapid but not abrupt return of skin temperature to the previous *high level (Fig 9)*

These findings may be compared with those obtained in normal feet made artificially hyperemic by the administration of a spinal anesthetic (Fig 12) In the latter the return to higher resting temperature takes place immediately the fan is switched off the interruption of vasoconstrictor tone is not due to denervation and there is no sensitization to adrenaline

At 59 days in case B1 the feet became cold after walking on stone floors Even after prolonged immersion of the arms in hot water

here was considerable delay in warming up particularly in the eft foot (Fig 7) From this time onward it was observed that whenever cooling with a fan was prolonged sufficiently to bring the skin temperature of the toes below a certain level (in this patient

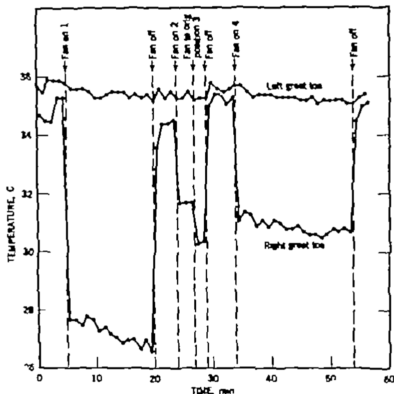


Fig 12 Effect of fan cooling normal feet after administration of a spinal anesthetic (90) Case BS1.

in the region of 24 C) they stayed cold If the fan was turned off before the skin temperature of the toes fell below the critical level the feet warmed up rapidly Following administration of insulin, if the temperature of the toes fell below the critical level they stayed cold even when the hypoglycemia passed off but provided the temperature of the toes had not fallen below this level the toes warmed up promptly soon after glucose was given (Fig 13)

However induced the algid state persisted until warmth from the environment or warmth conducted from proximal parts of the limb raised the skin temperature above the critical level. Then the skin

temperature rose more steeply indicating that relaxation of vessels had occurred. Once the feet were hot they tended to remain hot. The feet were sometimes not only cold-sensitive but heat-sensitive. If

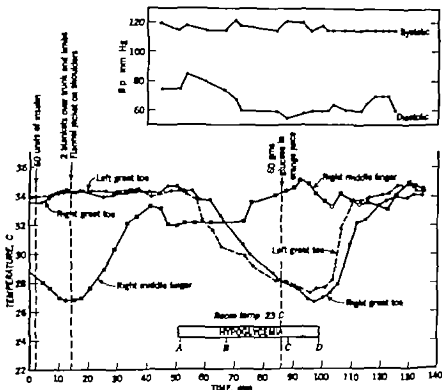


Fig. 13. Effect of insulin hypoglycemia in the hyperemic stage of immersion foot (90). Note pronounced fall in temperature of both toes with a slight rise in finger temperature during the period of hypoglycemia. Case B1 96 days after rescue.

the patient got into bed with cold feet, they stayed cold for hours, but once hot they felt excessively hot, so that he thrust them outside the bedclothes.

This instability of temperature may not be associated with any apparent changes in the appearance of the feet. In other cases there is a marked degree of cyanosis. Color changes on elevation and pendency may still be present but are less pronounced than in the earlier stages.

I have mentioned that even after immersion of the arms in hot water there may be a long delay before vasodilatation occurs Occasionally there is complete failure of reflex vasodilatation when the initial temperature of the feet is relatively high (24–26 C) This is apparently not due to obstruction in the cutaneous blood vessels, since the local injection of histamine causes a conspicuous rise in temperature (70)

In feet that were initially damaged to the extent of superficial gangrene there may be late sequels suggestive of vascular occlusion impaired pulsation in the peripheral arteries delay in healing of ulcers formed by blisters and the removal of gangrenous tissue and pain in the legs suggestive of intermittent claudication.

SWELLING BLISTERS AND GANGRENE

Swelling, first noticed during exposure often increases rapidly during the hyperemic stage especially if the parts have been warmed. The edema is tense and does not pit readily on pressure The edema fluid has a high protein content and is not a simple subcutaneous transudate (70)

Blisters and ecchymosis may develop with the increase in swelling The amount of blistering varies with the severity of the tissue damage Many mild and a few moderately severe cases do not show blisters Areas frequently affected are the toes the dorsum of the foot the calves and sometimes the soles Fluid from blisters is glairy or straw colored, and has a protein content similar to that of blood serum. Healing of blisters often takes from 3 to 6 weeks and occasionally several months

In many cases the skin of the hands and feet having become thick, hard and yellowish brown, desquamates completely during the first few weeks hairs may be lost toenails shed painlessly

Areas that will become gangrenous fail to warm remain white or blue, blister extensively at first and later become shriveled and black. In the early stages it is difficult to be certain of areas that will become gangrenous. Often the necrosis is only superficial later the dead tissue is shed, leaving pink healthy skin or at the worst, shallow ulcers. In this way complete thimble-like casts of the digits including the nails may be obtained. Extensive gangrene is rare, and even when an apparent line of demarcation encircles the limb or the base of a digit, it is by no means certain that all tissues distal

to this are gangrenous In one severe case, the distal parts of the foot separated after 7 weeks pain persisted and ultimately the legs had to be amputated.

BONES JOINTS AND TENDONS

Flatfoot is an occasional sequel but more often persistent wasting of the soft tissue of the sole produces an apparent accentuation of the medial plantar arch suggesting pes cavus.

A common deformity in immersion foot and trench foot is plantar flexion of the great toe with hyperextension and clawing of the small toes (For illustrations see ref 66 Figs 2 and 21) In severe cases permanent contracture may follow Hammer toe deformity of one or more digits is not uncommon even in cases of moderate severity

Roentgenograms may show decalcification of the bones of the foot—*diffuse or in rounded areas*—affecting the phalanges and the distal ends of the metatarsal bones similar to post traumatic osteoporosis. This condition tends to recover

SENSORY DISTURBANCES

With hyperemia comes pain usually burning, aching, or throbbing, but often with tingling or pins and needles The pain reaches a maximum in the first 24 to 30 hours is continuous and diffuse and may be referred to blisters or areas of incipient gangrene *Although this pain often lessens after 48 hours it may persist for several weeks.*

About the seventh to the tenth day after rescue the patient is liable to pains of another type These are shooting or stabbing pains not unlike the lightning pains of tabes dorsalis They occur at irregular intervals as sharp stabs like bursts of machine-gun fire, within the foot, or stabbing vertically from without. Worse at night, and often controlled only by morphine those pains are made worse by warmth. They sometimes begin after the first hot bath. Because of the pain or discomfort when the limbs are warm, the patient may thrust his feet outside the bedclothes Moderate cooling relieves the pain. The pains tend to be more prominent when the feet are pendent, after exercise, and when the feet are warming for example after getting into bed at night. *Exceptionally attacks of stabbing* pain may be precipitated by micturition, defecation, coughing, or yawning Gradually diminishing in intensity and frequency pains

and paresthesias *usually disappear within 6 to 14 weeks* but they may recur after prolonged standing or walking in cold or wet weather, even years after exposure

As hyperemia develops there is often rapid recovery of sensation After 12 hours limbs which in the prehyperemic stage were insensitive as high as the tibial tuberosity will show only a sock or slipper type of sensory loss Even the areas which remain insensitive to touch and pinprick may be hyperesthetic to light stroking and intolerant of the touch of bedclothes or dressings Within 7 to 10 days of rescue a relatively stable sensory pattern is obtained There is a loss of all modalities of sensation over a variable area of the feet and toes Typically the loss is of sock or carpet slipper distribution, but not infrequently additional areas of anesthesia are observed over pressure points such as the malleoli As a rule, analgesia to pinprick is slightly more extensive than anesthesia to *cotton*.

Once this stage is reached further progress depends on the extent and severity of the nerve lesions If the sensory loss is extensive recovery is slow and is dependent on the regrowth of nerve fibers The progress of sensory recovery in some typical cases is shown in Figures 1 3 5 and 14

MOTOR DISTURBANCES

In the early hyperemic stage, movements of the ankle and toes are hampered by swelling. As edema subsides weakness and wasting of the intrinsic muscles of the foot become apparent and the toes become clawed The wasted muscles exhibit diminished electric excitability When patients begin to walk they have a flatfooted and *springless gait Knee jerks are present,* and ankle jerks are nearly always obtainable Plantar reflexes are absent or flexor Wasting of the muscles may persist for a long time, even after there is a recovery of sensation and evidence that the muscles are reinnervated

SUDOMOTOR DISTURBANCES

At first the limb is dry over an extensive area but tests by the Guttmann method (48) show that the zone of true anhidrosis corresponds closely to the zone of analgesia to pinprick. During recovery sweating returns rather more quickly than appreciation of light touch and moderate pinprick.

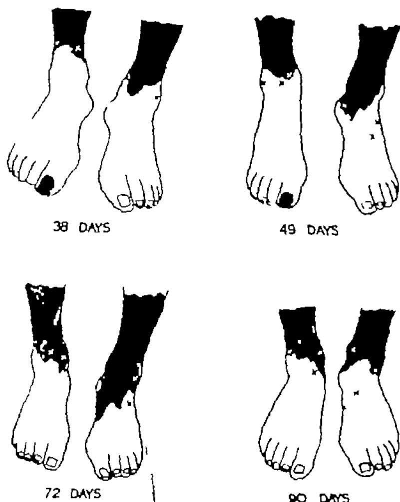


Fig 14 Distribution of sensory loss and of anhidrosis at intervals after rescue in patient with moderately severe immersion foot (right grade D6 left, grade C7) (90) Case IN6 Dotted line and crosses mark the upper levels for sensory loss to light touch of cotton and to moderate pinprick respectively Black areas indicate heavy sweating, dotted areas moderate sweating, and unshaded areas absence of sweating (sweat test by quinizarin method (43) In right great toe the black area indicates site of superficial gangrene.

A striking feature of the posthyperemic stage is the spontaneous occurrence of excessive sweating On a hot day socks are quickly soaked but even when cold the feet sweat excessively Sweat rashes are not uncommon in areas where sweating is heaviest. This hyperhidrosis is similar to that observed in causalgia and other irritative nerve lesions in that it is most obvious in response to emotional or painful stimuli whereas over the affected area thermoregulatory sweating may be diminished Sweating is often most pronounced at the margins of analgesia and anhidrotic areas this is the marginal hyperhidrosis described by Guttmann (48) It is evident in areas which were previously anhidrotic and which now show recovering sensation and hyperalgesia—the hyperhidrosis of recovery

Excessive sweating may be observed in relatively mild cases with little sensory loss. In a patient with unilateral immersion hand the hyperhidrosis was confined to the affected extremity and ceased after 4 months as the hand became reinnervated More often the hyperhidrosis persists for many years Hyperhidrotic feet are liable to blister after the patient returns to normal footwear and long walks

OTHER CLINICAL FINDINGS

Transient albuminuria may be present just after rescue Mild tachycardia and pyrexia up to 99.5 F may last for several weeks Even in the absence of sepsis more marked pyrexia may occur if tissue damage is extensive (19) Respiratory infections and alimentary disorders are rare A few days after rescue one patient had severe melena and later developed symptoms suggestive of a duodenal ulcer He had hyperchlorhydria but no ulcer was found on roentgenographic examination. A similar case has been described by Goldstone and Corbett (41)

Immersion Hand

In at least two-thirds of the patients with immersion foot the hands are also affected usually less severely In men with slight degrees of immersion foot, the incidence of immersion hand is about 50 per cent and the severity is minimal In severe degrees of immersion foot, the incidence rises to 90 per cent and severity also increases.

The hands are seldom continuously immersed but are nevertheless exposed to severe degrees of cold and wet Moreover general body cooling results in strong reflex vasoconstriction in the upper limbs Occasionally the hands are more severely affected than the feet Richards (70) described such a case Another example was seen in an aviator who spent 14 hours in a rubber dinghy He was clinging to the center rope of the dinghy and his hands were immersed as much as his feet (82)

In an aviator (case RF1) who had lain exposed for 22 hours on a snow-covered mountain the only affected extremity was his un gloved hand.

If the hands are used actively e g for rowing or bailing they are less likely to suffer damage and if one hand is more exposed or immobile than its fellow it will suffer more severely This has been noted particularly in patients who have used one hand to scoop up water or snow in order to quench their thirst

If air temperatures are very low nonimmersed hands may be frostbitten Immersion foot and frostbite of the fingers of the right hand were both observed in a patient who had been grasping a metal bailer

The clinical picture of immersion hand is similar to that of immersion foot. During exposure the hands are numb swollen and clumsy and survivors find it difficult to undo buckles or caps of flasks. After rescue, the hands become hot and throbbing and intense paresthesias are felt in the finger tips. Swelling is less than in the feet but when it subsides wasting of the intrinsic muscles is very prominent, the appearance presented being similar to that of progressive muscular atrophy (Fig 4) There appears to be a dissocia tion between motor and sensory functions as severe wasting may be present with little or no objective loss of sensation. Pain in the hands is uncommon but tingling persists for a long time and is most prominent when the hands are exposed to cold or are warming. Objective sensory findings as a rule are confined to hypoesthesia and hypalgesia of the finger tips. The skin assumes a dirty yellow color and desquamates leaving healthy pink skin Even in mild cases cold-sensitivity is common and in more severe cases attacks of Raynaud s phenomenon have been observed Hyperhidrosis is also prominent in the hands but subsides more rapidly than in the feet In the late stages although the hands may appear normal patients

complain that as soon as they are exposed to cold their hands become stiff numb and weak Critchley (25) has described permanent deformity of the fingers due to contraction of flexor tendons and atrophy of subcutaneous tissue.

Etiologic Factors

The essential cause of the syndrome is exposure of the limbs to cold insufficient to freeze the tissues. Sea water freezes at —1.9 C tissues do not freeze until their temperature falls to —2.5 C or less so that parts continuously immersed cannot be frostbitten. In most cases in our series the sea temperatures ranged from —1 9 to 12 C (An affection of the limbs in survivors adrift in warmer waters 18 to 26 C) will be considered separately) These figures are derived either from measurements made at the time or from data provided by the Royal Naval Meteorological Branch. When there was floating ice and the spray froze as it fell inboard the water temperature was judged to be approaching —1 9 C

The colder the water and the longer the exposure the greater is the damage. Factors more difficult to assess include the extent of the area cooled the susceptibility of the individual and the circulation in his extremities

In tropical waters where sea temperatures ranged from 18 to 26 C., men adrift for several weeks escaped with nothing more than transient swelling of the feet, although a few had symptoms and signs suggesting a minor degree of peripheral vasoneuropathy

With sea and air temperatures in the region of 10 C on the other hand men adrift in lifeboats had all developed immersion foot of greater or less degree after 10 to 15 days In a locality where sea and air temperatures were probably 8.3 C., men clinging to Carley floats soon died from exposure. The few who were rescued after 60 to 70 hours all suffered from immersion foot (grade B C or D)

At sea and air temperatures of 7.5 and 1.5 C., and also under very adverse conditions two aviators in a rubber dinghy developed peripheral vasoneuropathy (grades B and C) in as short a time as 14 hours.

Experimental immersion for 2 hours in water at 3.9 C has produced transient neurologic signs including anesthesia which did not entirely resolve within 3 hours, by which time the feet were warm (49)

Fausel and Hemphill (34) have described 65 patients many with immersion foot, in whom the duration of exposure ranged from 1 to 10 hours The water temperature varied from 28–38 F (−2.2 to +3.3 C.)

Peripheral vasoneuropathy may follow even shorter exposure Two men struggled in an icy sea off Murmansk for 20 minutes and were subsequently in an open boat for 10 minutes The probable temperature of the air in the region was −20 C and of the water −1.9 C. When I saw the patients 3 weeks later the condition of their feet was indistinguishable from immersion foot grade B4 or C5 One of the men had been clinging to floating ice with his left hand. This hand blistered extensively and later showed muscle weakness and wasting, and sensory disturbances characteristic of immersion hand.

In another instance, a man immersed for less than an hour sustained neural lesions affecting the hands and feet, symptoms of which had not entirely disappeared 6 months later

Stray (81) and Denny Brown *et al* (27) have produced evidence that cooling short of freezing for periods of about an hour or less may damage peripheral nerves (see "Pathogenesis")

It will be noted that the incidence and severity of immersion foot, even among men in the same boat may vary widely Such variations are due to (*1*) personal and local environmental differences such as clothing, exercise and recent food intake which affect the degree of cooling or influence the peripheral circulation (*2*) factors such as shock or illness which lower a man's resistance and (*3*) basic differences between individuals in their susceptibility to the local and general effects of cold.

During short exposure footwear affords some protection, but during long exposure boots constrict swelling feet and impair their circulation, so that a booted foot often s[illegible] more than a bootless one *Rubber boots give no better protect*[illegible] leather ones, even if they do not fill with water the feet [illegible] [illegible]em soon become [illegible] with sweat.

Relative immobility and continu[illegible] of the feet a[illegible] portant factors probably because [illegible] arterial infl[illegible] venou[illegible] Mechanical interfer[illegible] circulation ample [illegible]lothing, constrict[illegible] continued from t[illegible] seat, also accer[illegible] [illegible]tion. C[illegible] the up[illegible] [illegible]e body by wind [illegible]inadeq[illegible] ing, act[illegible] [illegible] peripheral

Starvation dehydration shock, nutritional deficiencies, seasickness—these conditions affect either the resistance of the tissues or their blood supply Three out of four patients in whom peripheral vasoneuropathy developed at sea without actual immersion had suffered severely from seasickness The susceptibility of individual limbs may be increased by previous cold injury or by any other condition which impairs the local circulation.

Basic differences in the susceptibility of the individual to the general and local effects of cold may be related to race, heredity, age body build texture and color of the skin moisture and fat content in the skin thickness of subcutaneous fat and so on. For example Stray (81) found differences between blondes and brunettes in skin temperature on the face and ears and in the incidence of frostbite

Many survivors have remarked that those who lost heart died more quickly or suffered more severely than their companions The few men over 40 and under 17 seemed to die from cold sooner than those of intermediate age Within the main group age and severity were not closely correlated. Colored races are said to be more prone to trench foot. In Webster's series (92) those who suffered most were Greeks Negroes Australians and men employed in the engine room and stokehold that is those accustomed to a warm environment. In our series however Arab firemen suffered no more severely than European deck hands

Probably the most important factor influencing individual susceptibility is the peripheral blood flow Persons with an unstable vasomotor system in whom cold or anxiety readily induce strong peripheral vasoconstrictions are said to be more susceptible to trench foot. Tobacco because of its tendency to cause vasospasm might be expected to play a part but no proof of this has been adduced Stray (81) found that indoor workers were more susceptible to frostbite than outdoor workers The possibility of acclimatising the extremities to cold is suggested by the work of Kerr (51) Men coming from warm climates or hot engine rooms are said to be particularly susceptible to immersion foot, but this has not been our experience During exposure to cold, the body conserves heat at the expense of the extremities by diminishing their blood supply In persons acclimatised to heat this mechanism does not operate efficiently until the blood volume has been reduced by diuresis Meanwhile the hands and feet get a larger blood flow than would otherwise be the case This

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Relative immobility and continued pendency of the feet are important factors probably because they affect arterial inflow and venous return. Mechanical interference with the circulation for example by tight clothing constricting boots or continued pressure from the edge of a seat, also accentuates the condition. Chilling of the upper parts of the body by wind and water and inadequate clothing, act by reducing the peripheral circulation

Starvation dehydration shock, nutritional deficiencies seasickness—these conditions affect either the resistance of the tissues or their blood supply Three out of four patients in whom peripheral vasoneuropathy developed at sea, without actual immersion had suffered severely from seasickness The susceptibility of individual limbs may be increased by previous cold injury or by any other condition which impairs the local circulation.

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perhaps accounts for the fact that in our series the incidence of immersion foot was no higher in engine room personnel than in deck hands.

The resistance of individual tissues varies, nerve and muscle being particularly susceptible. The susceptibility of muscle in particular is probably influenced by its state of nutrition and metabolism at the time with respect to such factors as hydrogen ion concentration, mineral balance, enzyme activity and the presence of harmful metabolites resulting from fatigue. Although the skin gets the brunt of the damage in frostbite, it is on the whole remarkably resistant to cold short of actual freezing. The minute vessels are readily damaged by intense cold although relatively little affected by prolonged cooling of lesser degree. The susceptibility of individual tissues will be discussed further under "Pathogenesis".

Immersion has no specific action apart from its effect in increasing the rate of heat loss and is not an essential factor. The disorder may arise in extremities exposed to prolonged cold with no more damp than is provided by condensed perspiration. We have seen a number of cases of so-called "seaboot foot" in men serving in ships on North Atlantic and Arctic convoys. In some instances at least, the degree of cold was not such as to have caused frostbite and the condition has been observed with temperatures as high as 8 to 12 C. Men affected were those who remained relatively immobile on the bridge or on small gun platforms seldom for more than 4 hours at a time. After several days, during which they had usually worn rubber sea boots continuously, the feet became red, painful and tender. They walked as though on hot bricks. In light cases a change to leather footwear was followed by recovery in 3 or 4 days (23). In more severe cases (e.g. case Tr2, page 270–1) there were usually contributory factors such as boots which had become tight, too rapid warming of the feet, seasickness and in one instance hemorrhage and shock from wounds.

Other cases in which the immersion foot syndrome occurred without actual immersion include an injured aviator exposed for 40 hours in snow whose hands and feet were affected (70), an injured aviator lying for 22 hours in the snow whose exposed left hand was the only extremity involved (89), a bus driver whose feet suffered (39) and a deserter from the army who spent 8 days in a cold pillbox and sustained severe vasoneuropathy with gangrene of the toes (70). Such

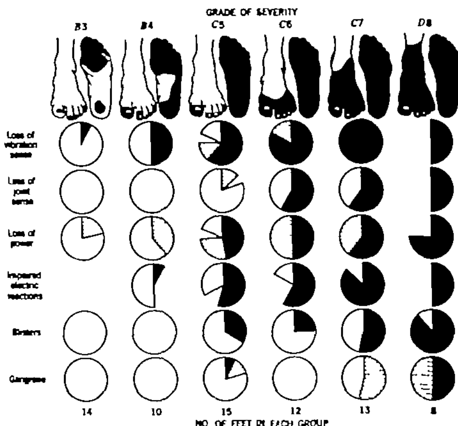


Fig. 15. Classification of cases of immersion foot according to extent of anesthesia at 7 to 10 days after rescue (90) Extent of anesthesia is closely correlated with severity in other respects. In the circles, black areas indicate proportion of feet affected in each group stippled areas refer to partial defects, or to superficial as opposed to deep gangrene. Gaps in the circles correspond to feet which were not tested. The whole of grade D9 has been omitted, as gangrene prevented many of the tests.

cases are included along with trench foot seaboot foot, immersion foot, and immersion hand, under the one comprehensive term "peripheral vasoneuropathy after chilling."

Grades of Severity

Webster *et al* (92) divided their cases into 4 groups according to the degree of edema, blistering ecchymosis etc the most severe cases had massive extravasation of blood and incipient gangrene. Brownrigg (19) also graded his cases with special emphasis on

blisters and gangrene In my own experience (87) the most significant factor in prognosis is the amount of damage to peripheral nerves A useful criterion is the extent of loss of sensation to touches with cotton at the end of the first week after rescue. To obtain a quantitative estimate of anesthesia the following method was adopted the foot and leg were divided into a number of arbitrary geometric areas sensation to touches with cotton was tested in each of these areas, and the number of areas from which a response was not obtained was taken as an index of anesthesia. On this basis, cases have been subdivided into 9 groups.

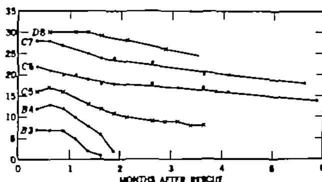


Fig. 16 Average rate of recovery of sensory loss to light touch of cotton in cases with various degrees of severity Sensory loss was charted as in Figure 1. The number of feet in each group is indicated in Figure 15

The extent of the anesthesia and the correlation between this and the severity of the other symptoms in each group is demonstrated in Figure 15 In groups 3 and 4 nerve damage is designated "reversible" because symptoms and signs disappear within 4 to 9 weeks—a period which is too short to permit any extensive regrowth of nerve fibers (see Figs 16 and 17) In groups 5 to 9 on the other hand recovery is slow and is considered to take place by regrowth of axons, nerve damage in this group is therefore regarded as "irreversible" or "degenerative" On this latter basis, a somewhat broader classification appears justifiable as follows

Grade A. Minimal Cases without Interference (or with Transient Interference) with Nerve Function. In this group of cases the feet are swollen for a few days, and there may be transient

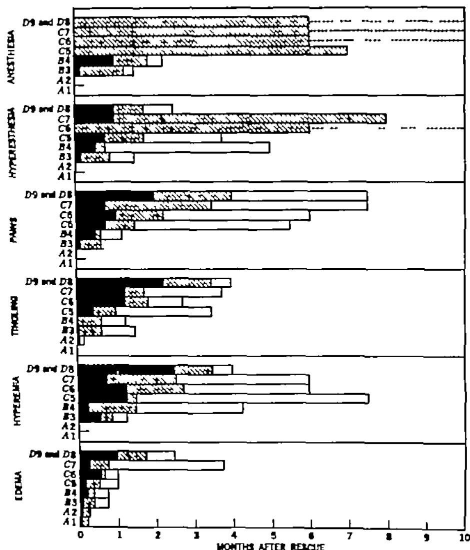


Fig. 17 Duration of symptoms and signs according to degree of severity (90) Black areas, minimum duration shaded areas, average duration unshaded areas, maximum duration. In groups where there was considerable anesthesia or hyperesthesia at the final examination 6 months after rescue, maximal or minimal times cannot be indicated and the columns are prolonged by a dotted line.

tingling. Both features subside within a week. In a few instances pains develop in the second week. Late sequels are rare, but there may be some cold-sensitivity

Grade B Mild Cases with Reversible Nerve Damage. Anesthesia is confined to parts of the plantar surfaces of the feet and the tips of the toes, and disappears in 4 to 9 weeks. In the great toes vibration sense is lost in about 25 per cent of cases but position sense is not affected Weakness of the intrinsic muscles of the feet may be present for a few weeks but there is seldom wasting or impairment of electric excitability Edema lasts 1 to 3 weeks hyperemia, 3 to 7 weeks tingling, pain, and hyperesthesia last 2 to 4 weeks. Blisters and gangrene do not appear in this group Sooner or later about half the patients complain of excessive sweating of the feet, and in a similar number the parts are cold-sensitive. The stay in hospital is 4 to 8 weeks and men return to full duty ashore or afloat within 3 to 4 months of rescue.

Grade C. Moderately Severe Cases with Irreversible (Degenerative) Nerve Lesions. In this group there is complete anesthesia of the plantar surfaces of the feet the dorsum and sides of the feet are involved to an extent varying from the distal segments of the toes to a level just distal to the ankle joints Vibration sense is nearly always absent in the great toes and position sense much impaired Wasting of the intrinsic muscles with loss of power and impaired electric reactions are present. Edema lasts 2 to 3 weeks tingling, 4 to 8 weeks stabbing pains and hyperemia last 5 to 14 weeks and hyperesthesia lasts 6 to 8 weeks or longer in severe cases. Blisters develop in about half the cases and superficial gangrene may occur Sensory loss and motor disorders persist for many months at 6 months the extent of the anesthesia is still considerable. Later hyperhidrosis and cold-sensitivity develop in rather more than half the cases Recurrence of pains, tingling, and swelling is common. The stay in hospital for patients in this group is 8 weeks to 6 months. In time, more than half the patients recover sufficiently to return to full duty and only about one-quarter have to be invalided from the service.

Grade D Severe Cases with Irreversible (Degenerative) Nerve Lesions and Gangrene. In this group anesthesia covers the whole foot to above the level of the malleoli. Such toes as are available for testing show loss of vibration and position sense. The small muscles of the feet are wasted and paralyzed. Edema lasts from 3 to 7 weeks tingling pains and hyperemia last 3 to 4 months. Blisters appear in the feet and legs, and gangrene invariably

develops usually resulting in the loss of digits. In the later stages gangrene is complicated by sepsis, and amputation may be necessary Most patients spend at least 6 months in hospital, and even at the end of that period are severely disabled Very few become fit even for the lightest of service duties.

Edema of Limbs in Survivors from Shipwreck in Warm Waters

Even in the tropics, edema of the feet may follow prolonged exposure in open boats or on rafts There were three incidents in the present series in which men adrift in warm waters (18–26 C) were affected in this way Factors involved include relative immobility and pendency of the feet, immersion in warm sea water semistarvation, dehydration and the effects of strong sunlight. From a consideration of these cases and those described by White (94) it is apparent that we are not dealing with a simple clinical entity

The cases fall into two main groups In one the clinical picture resembles mild peripheral vasoneuropathy after chilling. In the other acute nutritional deficiencies and dehydration are prominent features and there is nothing to suggest tissue damage by cold.

In the first group symptoms and signs recall those seen in immersion foot of mild degree. Edema and perhaps numbness begin during the first few days of exposure followed after rescue by hyperemia tingling shooting pains (which may be delayed 5 or 10 days) plantar tenderness and sensory loss in distal parts of the feet. The hands may be affected too although less severely There may be no signs of acute nutritional deficiency or of gross dehydration. Moreover the fact that symptoms sometimes begin after only 2 days adrift speaks against a purely nutritional cause. Sunburn, "salt water boils," and infection from abrasions might account for some of the heat, redness and edema, but not for the neural symptoms. Immersion in sea water even at temperatures as high as 18 to 26 C will presumably produce some cooling of the deeper tissues. Moreover survivors adrift in tropical waters, although suffering from intense heat during the day often shiver with cold during the night. The findings suggest that prolonged immersion in sea water at these temperatures together with contributory factors such as relative immobility and continued pendency of the feet and periodic body cooling with consequent reflex vasoconstriction, may be sufficient to cause a mild degree of peripheral vasoneuropathy after chilling.

The other group includes survivors subjected to semistarvation and severe dehydration for 2 weeks or more Swelling may not become evident until a day or two after rescue. Sensory disturbances if any are usually slight and transient. There may be depletion of plasma proteins and signs such as glossitis, stomatitis paresthesia, tender calves, and circulatory changes suggesting vitamin deficiency From the work of Lewis (60) it is clear that immersion of the limbs in warm water together with continued pendency and lack of exercise are in themselves enough to cause edema The effect, which is not due to inhibition, is least at about 18 C and increases as the temperature rises above this level When edema appears only after rescue, when it persists for long periods or when sensory disturbances are present, other explanations must be sought. It is possible as White (94) suggests, that vitamin deficiencies may be brought about in relatively short periods by subsistence on a low unbalanced diet with very little water during exposure to strong sunlight. Dehydration might account for the nonappearance of edema until a day or two after rescue, when fluid intake is increased. In one instance, however edema recurred whenever the feet became hot over a period of 21 months, despite vitamin B_1 therapy and normal plasma protein levels The possibility remains that small vessels in the extremities are damaged and rendered more permeable by one or more of the conditions of exposure—dehydration, undernutrition prolonged immersion, and strong sunlight.

Frostbite—Differentiation from Immersion Foot

Some authorities hold that there is no real distinction between frostbite and immersion foot. This may be true of portions of tissue examined histologically but, when the picture is reviewed as a whole wide differences are apparent.

The distinction is important. Frostbite occurs in dry air which is a poor conductor of heat. Extreme cold is necessary to produce damage in such an environment, but the duration of the exposure need be only a matter of minutes. The damage occurs when supercooling gives place to freezing and solidification. Effects which depend on the duration and intensity of the freeze, range from quickly transient symptoms—such as pain or swelling—to deep gangrene.

A severe and rapid freeze causes the death of all tissues in the area, regardless of their biologic resistance. If the skin suffers most, it is because it is the most exposed

A less severe freeze causes damage to the minute vessels, the results of which overshadow other findings. Exudation of plasma leaves the vessels silted up with cell masses so that stasis results. If stasis persists the cell masses become organized as thrombi and gangrene ensues. There is little damage to nerves except in, or close to, the necrotic area. Even with necrosis of the whole thickness of the digit, I have found the adjacent skin after a few weeks sensitive to touch and pinprick, and responsive to vasomotor control. If gangrene is prevented by heparin, nerves in areas which would otherwise have been necrotic show evidence of damage in the form of anesthesia and paralysis lasting several weeks (55) Thus the nerves are no less vulnerable to freezing than other tissues but the nerve damage is well localized and tends to be overshadowed by the effects of injury to the skin and its minute vessels.

Immersion foot and trench foot, by contrast, occur in a wet, moderately cold environment. Water is a good conductor of heat, and permits chilling throughout the depth of the extremity which may be continued for days or weeks Prolonged chilling and ischemia affect chiefly the tissues with the weakest biologic resistance (nerve and muscle) Damage to vessels is relatively slight, even with extensive irreversible nerve damage there may be no loss of skin.

Differences are most easily seen when the two conditions coexist, as in men who had been adrift in Arctic waters and sustained frostbitten hands and immersion feet. Their hands, exposed to air temperatures often in the region of —20 C became frostbitten, usually after contact with metal objects Their feet, immersed and thereby protected from freezing, suffered the effects of prolonged but less intense cooling. A few weeks later certain finger ends were gangrenous, but the skin right up to the line of demarcation was sensitive to touch and to pinprick, and vasomotor responses were obtainable. In the feet there was little or no gangrene, at the most, superficial blackening of the skin of one or two toes, but anesthesia (and anhidrosis) extended almost to the malleoli with paralysis of the feet, and complete vasomotor paralysis in the digital vessels Case IN6 (Fig. 14) is an example.

In some cases no clear distinction was possible, the limbs having been subjected to both rapid and slow cooling, resulting in a

combination of frostbite and immersion foot or something inter mediate between the two.

In another incident, already referred to 2 men struggled for 20 minutes in the icy sea off Murmansk. One of them was clinging to floating ice After rescue, they spent another 10 minutes in an open boat exposed to very cold air Both developed edema, blisters, and signs of nerve damage in the extremities but neuropathy was most marked in the hand which had grasped the floating ice. The short period of exposure and the coldness of the air suggested frostbite but the clinical features were those of immersion foot and immersion hand Cases of this nature are exceptional but they suggest that the borderline between chilling and freezing may not be so clear-cut as has hitherto been believed.

Morbid Anatomy

Specimens obtained at biopsy amputation and autopsy have been examined and described by Blackwood (13a) The most severe in jury was to nerve and muscle.

Zenker's hyaline necrosis was seen in the foot muscles of a man who died during exposure (case B3 see under case B1 page 279,280) Chronologically the next specimen of muscle available for study was from a case of immersion foot 4 months after exposure In the experi mental animal (14), the early part of this interval was occupied by inflammatory changes in the necrotic muscle fibers resulting in the production of slender hypernucleated fibers. A similar process prob- ably occurs in man but of this there is no histologic proof From 4 months onward the changes were indistinguishable from those due to denervation and were associated with severe degeneration of nerves in the muscles. From 12 months onward, there was evidence of reinnervation and in some cases of restoration to normal.

Fibrosis of muscle is not a prominent feature, but muscles damaged during exposure become fragile and are apt to tear This may result in intramuscular hemorrhages and scar formation. Friedman (38) reports that encapsulated infarcts, probably due to vascular occlu sions and resembling those described in cases of Volkmann's contrac- ture were present as early as 32 days after exposure (case 5)

Patchy Wallerian degeneration, most marked in the distal portions of the nerves, was present in all cases surviving exposure. In 3 early cases of his series Friedman (38) found damage to the large medul

lated rather than the small nonmyelinated fibers. The destruction of myelin and lipoid phagocytes was so striking in his cases and in those of Siegmund (73) that damage predominantly to medullated fibers seemed indicated He suggests that injury to myelin may be due to the direct action of cold On the other hand Blackwood (13b), commenting on his earlier paper (13a), remarks that when the nerve injury was subtotal large myelinated fibers were among those surviving exposure, suggesting that the pathologic process does not selectively attack the large myelinated fibers

Regeneration was present in the later cases, 3 of which allowed an estimation to be made of the rate of regeneration. This was slow but not unduly so.

As after peripheral nerve injury, if regeneration is long delayed endoneural and perineural fibrosis may occur Otherwise marked fibrosis of nerves was seldom found in Blackwood's series and then only in relation to gangrenous or infected extremities. On the other hand, White and Warren (96) have described marked fibrosis in and around cutaneous nerves removed at biopsy from patients with immersion foot whose neuritic pains had persisted for many months after exposure. Friedman (38) also found perineural fibrosis with exaggeration of the epineurium and perineurium (the example given, case 11 was complicated by gangrene and infection) Occasional nerve bundles were partially or completely hyalinized. Many small blood vessels in the nerves were thickened. The degeneration and phagocytosis seen in the subcutaneous adipose tissue were also evident in the epineural fat.

Friedman's early cases showed degeneration of the epidermis and sweat glands. There was leukocytic infiltration and lipoid phagocytosis in the subcutaneous fat which in late cases was replaced by fibrous tissue. Atrophy of fat may be partly responsible for the wasting of plantar tissues so frequently evident in immersion foot. "Lardaceous inflammation' following the exudation of a fluid rich in protein would account for the inelasticity and rigidity of tissues and restriction of movement in the digits noted in some cases Blackwood found early osteoporosis followed by the deposition of new bone subperiosteally and around the haversian canals.

Arterial changes were very slight and did not differ significantly from the expected normal for hard living men (13a) This is a point of distinction from frostbite a recognized sequel to which is oblitera

tive endarteritis (30) Damage to capillaries and veins was usually restricted to areas adjacent to gangrenous or infected tissue (see "Pathogenesis" below)

Pathogenesis

Since this subject was last reviewed (90), the cessation of hostilities has facilitated access to wartime publications and opportunities have arisen for discussion with workers in Europe and America

Three main causal factors require consideration (*1*) direct effects of cold, (*2*) effect of anoxia and (*3*) pressure from exudation of fluid into the tissues.

It is also important to consider how much damage occurs during exposure and how much in the process of return to normal temperature. During exposure there is little exudation and damage is presumably the result of cold itself or of anoxia resulting from vasoconstriction and the diminished dissociation of oxygen at low temperatures. During the process of return to normal temperature there is also danger of anoxia, from "silting" and other causes, as well as considerable exudation into the tissues.

DIRECT EFFECT OF COLD ON THE TISSUES

Certain tissues isolated from the body have a remarkable resistance to cold. Human spermatozoa have regained motility after 3 hours in liquid helium at —269 to —270 C., only 3 or 4 degrees above absolute zero (50)

Skin frozen at —72 C., dried and kept for 17 days, has regained after grafting, the appearance of normal skin (91) Dog's legs amputated at midthigh level and kept in cracked ice for 24 hours, have been successfully regrafted (16) A hibernating bat can be stored for several weeks at 0 to 2 C. and after warming fly away unharmed (63)

Lake (53,54) has shown that for tissues *in vitro* there is a critical temperature level in the region of —6 C at which irreversible changes, probably of a physicochemical nature occur after cooling to this level, recovery is impossible. Intact tissues, however possess the property of supercooling and may be cooled to a lower level before actual freezing occurs (61)

Freezing to solidification does not necessarily entail major tissue damage. Kreyberg (52) remarks

" It is reasonable to believe that the formation of ice crystals in the tissue represents an additional mechanical or physical insult to the cold proper But for the end result it may be that this physical factor is of minor importance "

In frostbite freezing has occurred there is a central zone of devitalized tissue surrounded by a zone in which tissue damage is minimal. Immersion foot is due to chilling of the tissues without freezing Opinions differ as to the amount of damage that may be done by cooling to temperatures within the range (—1.9 to 12 C) which causes immersion foot. Indeed chilling of limbs to similar temperatures is used in the treatment of burns gangrene, and peripheral sepsis (2,3)

With respect to refrigeration anesthesia, Allen claims that the tourniquet actually prevents tissue damage by cold the ischemic limb behaving like isolated tissue. He suggests that many of the ill effects of cold are due less to the cold itself than to a breakdown of the body's defenses He cites Fay (35) who by artificial hibernation has kept patients at rectal temperatures near 26 C for 5 to 8 days Without narcotics such patients in an effort to maintain their body temperature would die of exhaustion from shivering.

One argument advanced by those who believe that the effects of cold of this degree (—1.9 to 12 C) are per se harmless to the tissues rests upon the results obtained by Lake (53,54) in his tissue cultures. As the scale of temperature is decreased anabolism ceases before catabolism. In the zone between 25 and 10 C., the products of tissue catabolism accumulate. At temperatures about zero metabolism ceases and the tissues, requiring neither oxygen nor nutriment, can not suffer from ischemia. These observations suggest that damage to chilled limbs occurs not while the temperature of the tissue is low but while the temperature is falling or rising through the zone of imbalanced metabolism between 10 and 25 C Metabolites which accumulate during this phase are responsible for the initial intense vasodilatation which follows exudation results and is responsible for the neurologic and nutritional lesions.

It is doubtful if this hypothesis based upon observations on isolated tissues, is applicable to the human limb The pathologic studies of Smith Ritchie and Dawson (75) Blackwood and Russell (14) Blackwood (12) and Friedman (38) suggest that direct damage to tissue occurs during the period of low temperature.

Greene (46a) and *Lake* (53,54) beleive that in both immersion foot and trench foot little or no damage is done during the period of exposure and that harm is done chiefly during the period of thawing.

EFFECT OF ISCHEMIA

The clinical results of ischemia seen in conditions such as traumatic arterial spasm and tourniquet paralysis are in many ways similar to those of immersion foot. The extremity which has its blood supply cut off or seriously reduced for several hours by spasm of the main artery or the prolonged application of a tourniquet, is probably placed in a position somewhat analogous to that of an extremity exposed to cold. In the latter the deprivation of blood supply is less acute, and an additional effect of cold will be to mitigate or delay changes in the tissues by reducing metabolism. The reactive hyperemia which follows a period of circulatory arrest has its counterpart in the early hyperemic stage of immersion foot. The sensory findings in cases of immersion foot are very similar to those described by Parkes (65) in cases of ischemia. In a patient with tourniquet paralysis whom I observed, the resemblance was made more striking by the development, on the eleventh day of stabbing pains like those which occur in immersion foot.

EFFECT OF EXUDATION

The theory that the symptoms of immersion foot are due to pressure from the excessive exudation which accompanies the hyperemic stage lacks support. There is no other clinical condition in which unrestricted swelling of a limb causes vascular and neurologic symptoms comparable to those of immersion foot.

We therefore suggest that immersion foot is a vasoneuropathy resulting from a combination of chilling and partial ischemia. The role of these factors in the production of certain symptoms and signs will now be considered.

EFFECT OF COLD ON BLOOD VESSELS

Physiologic and Early Defensive Reactions. *Skin Color* The following account of changes is based chiefly on the findings of Lewis (57–59), Stray (81) and Kreyberg (52)

The first response of the skin to cold is pallor due to vasoconstriction of minute vessels as well as of the arteries and veins. At a level somewhere between 25 and 15 C., the skin becomes blue. The minute vessels are somewhat dilated and the arteries and arterioles somewhat constricted From 15 C downward, the skin becomes increasingly red.

At 10 C., the skin is definitely red The minute vessels are dilated and filled with oxygenated hemoglobin. The flow is sluggish due to constriction of the stronger arterioles. The small arteriovenous differences in oxygen content observed at low temperatures (5 47) are due to shunting through arteriovenous anastomoses and to diminished dissociation of oxygen at low temperatures.

Below 10 C the skin is bright pink until freezing temperatures are approached, when constriction of the minute vessels gives rise to the white reaction (81) This is not to be confused with the whiteness of frozen tissue, which is due to loss of transparency from ice crystals.

Blood Flow Vasoconstriction in response to cold is a complex reaction (59) First there is the local, direct and persistent response of the superficial vessels to cold. This is independent of nerve impulses and is associated with decreased permeability (55) Second there is general vasoconstriction, a reflex to cold applied to any part of the body's surface. This is transient. It is succeeded and replaced by a third response sustained general vasoconstriction due to cooled blood reaching the brain and acting on a central nervous mechanism. These vasoconstrictions involve all surface vessels—arteries arterioles, capillaries venules and veins, as well as the arteriovenous anastomoses. Thus body heat is conserved at the expense of the immersed limb The result is further cooling of the limb which leads to still further vasoconstriction of the contained vessels

This vicious circle is interrupted by periodic vasodilatation, which is part of the skin's local defense Immersion in water brings the skin near to the temperature of its surroundings in a very few minutes In the case of fingers or toes immersed in water below 10 C., vasoconstriction gives place at intervals to periods of vasodilatation involving the arteriovenous anastomoses, in which the temperature of the part may rise as much as 5 to 8 C This periodic vasodilatation, which may fail to occur in limbs more deeply immersed results in a distinct increase in the mean blood flow through the part Not only skin temperature readings but plethysmographic records indi

cate that in an immersed extremity the blood flow is lowest in water at 15 to 20 C and that *it increases progressively as the water temperature falls* below 10 C (77 78) Other signs of response to injury such as pain swelling, local redness, flare, wheal or even blister can be elicited by the application of cold from 15 C (occasionally 18 C) downward.

Lewis (59) measured the swelling of hands immersed in water at various temperatures At low temperatures the exudate had a high protein content. Spealman (79) made similar observations in subjects sitting at a room temperature of 16 C with one foot in water for 2 $^1/_2$ hours. In moderately cold water (15 to 25 C) the feet showed little change in volume In warmer water (30 C) or colder water (10 C and below) swelling was considerable. Swelling due to cold increased with continued exposure, but regressed when the feet were placed in water at 20 C Pain and redness occurred in cold water only when swelling developed.

In other experiments (79) subjects sat for 30 hours in a cold room (16 C) with one foot immersed in ice water (0.5 C) but protected by a cellular rubber boot. A thin boot allowed the feet to cool to 12 to 14 C a point at which pain and swelling were very pronounced. Swelling disappeared within 2 or 3 hours and subsequently there was no pain or sensory impairment. Evidently feet must be colder than 12 to 14 C for damage to occur within a day or so Keeping the body warm greatly aided in keeping the feet warm. Exercising the foot within the boot was also of value.

With this account of the immediate effects of immersion, we pass the borderline between physiologic and pathologic reactions

Vascular Changes during Exposure and in the Prehyperemic Stage. *Vasoconstriction.* Whereas a foot immersed experimentally in water below 10 C is commonly red and has an increased blood flow the limb in the prehyperemic stage of immersion foot is pale and pulseless and the veins are collapsed. There is good reason for this ischemic state. The shipwreck survivor suffers chilling not merely of his feet but of his whole body often for days on end. This presumably causes strong vasoconstriction in proximal as well as in distal vessels, and prevents or limits the increase in blood flow normally observed in cooled extremities

In Raynaud's phenomenon, vasoconstriction is sufficient to cause complete vascular stasis in a digit. It is therefore justifiable to

assume that in immersion foot vasoconstriction is in itself capable of cutting off the blood supply to the chilled extremity Unless metabolism is in abeyance during this phase, partial or complete ischemia must occur In the early stages, at least, the ischemia is probably partial or intermittent, since the foot swells there must be enough blood flowing to permit exudation.

Thrombosis This is not an essential feature Even prolonged and apparently complete stasis may occur without subsequent thrombosis. Talbott (83) found that during general hypothermia although for many hours peripheral pulses might be impalpable and blood pressure unrecordable, thrombosis did not occur That the ischemic state of the extremity in the prehyperemic stage of immersion foot is due to vasoconstriction and not to organic vascular obstruction is clear, for in a few hours the limb becomes hot and pink with bounding pulses and there is every evidence of an active circulation

Except in relation to gangrenous or infected extremities, pathologic material from immersion foot has shown no evidence of organic obstruction of the main blood vessels (13 14)

We conclude that during exposure and in the prehyperemic phase of immersion foot, the predominant feature is vasoconstriction of both arteries and veins. The minute vessels may be constricted (pale skin) dilated (blue or occasionally red skin) or dilated in some areas and not in others (mottled skin) Because of the cold environment, the cooling of the body and the depth to which the limbs are immersed, the normal increase in blood flow is prevented by constriction of the proximal vessels Vasoconstriction may be sufficient to shut off the blood supply completely as occurs in Raynaud's phenomenon. More probably there is small intermittent flow of blood, since without it exudation could not occur

Hyperemic Stage. Transition to the hyperemic stage occurs when the warmth of the body and proximal parts of the limb has overcome the reflex vasoconstriction induced by cold. The chilled extremities themselves (which presumably are not directly heated) must attain sufficient warmth from the environment, and by conduction from proximal parts of the limbs, to release that vasoconstriction which results from the direct effect of cold on the vessels. The result is hyperemia which spreads from above and may reach the toes within an hour This recalls the vasodilatation induced by removal of vasoconstrictor tone in a cold but otherwise normal limb

The level of skin temperature attained is similar namely 34 to 35 C but it does not follow that blood flow is comparable. Normally during reflex vasodilatation blood flow through the digits may increase from under 1 ml to over 90 ml per 100 ml of tissue per minute. Up to a point, the change is reflected in a rapid rise in skin temperature —often more than 1 C. per minute Once a level of 34 to 35 C is reached, however a considerable increase in blood flow may occur without any significant further rise in skin temperature. In immersion foot, the findings point to an extremely active circulation plethysmography would probably reveal a blood flow considerably greater than that which results from simple interruption of vasoconstrictor impulses The full bounding pulses and the high skin temperature indicate dilated arteries and arterioles and probably arteriovenous shunts. The rapid filling and emptying of the veins and the normal venous pattern indicate that the veins are wide open. The fact that the intensity of skin color deepens rapidly on pendency and blanches on elevation indicates that the minute vessels are widely dilated and atonic—they fill and empty passively

The excessive vasodilatation which is present in the hyperemic stage may be due to three factors inflammation with the release of vasodilator metabolites, local damage to vessels, and vasoconstrictor paralysis

Lewis (59) demonstrated that an aseptic type of inflammation occurs in tissues exposed to cold. Vasodilatation after a brief period of exposure to cold is due to an axon reflex producing a relatively stable vasodilator substance similar to histamine. A similar vasodilator substance is also produced in ischemic tissues and is responsible for the phenomenon of reactive hyperemia (57) Freeman (37) showed that the duration of this hyperemia varies with the duration of the preceding ischemia and is such that the oxygen debt is repaid An accumulation of vasodilator metabolites may well boost the initial hyperemia, but once an active circulation is established these will be rapidly washed away from the tissues. Unless substances continue to be released they cannot be the cause of a vasodilatation, the duration of which is measured in weeks rather than days. Bacterial infection does not play a part in the early stages of the hyperemic phase but may be a factor in the presence of blisters ulcers, and gangrene. Metabolic requirements for tissue repair will also influence blood flow

Blood vessels may be damaged either directly by cold or from ischemia. In early cases, Friedman (38) found marked dilatation of minute cutaneous vessels although in later cases Blackwood (13) did not find any significant changes The remarkable alternations of skin color on elevation and pendency of the feet and the presence of petechiae and swelling indicate that the walls of the minute cutaneous vessels are damaged Some of this damage probably occurs during exposure and is accentuated by the sudden increase in blood flow during the onset of the hyperemia. The question of damage to the minute vessels will be considered again later, in relation to the causation of gangrene (page 319–320)

In both experimental and human biopsy material severe damage to peripheral nerves is present (14,15 13) In the main nerves of the foot the majority of the fibers are degenerated and of the few which escape many are of large caliber Sympathetic vasoconstrictor fibers are of small caliber and although affected late in ischemia, are relatively susceptible to cold (7) and are therefore unlikely to escape. The blood vessels of the foot are thus subjected to a form of postganglionic sympathectomy A week after exposure skin temperature gradients from affected limbs are very similar to those from sympathectomized limbs. The standard sympathectomy performed for the lower limb is predominantly preganglionic and it is unwise to strain this comparison. Complete division of the sciatic nerve results in the interruption of all postganglionic sympathetic fibers to the foot (except for a few in the long saphenous nerve) Such lesions produce a complete vasomotor paralysis in the toes resulting in a foot initially warm and pale, but later varying in temperature with that of the environment. The initial hyperemia lasts about 21 days (70) In immersion foot, denervation and tissue damage coexist, and the hyperemia may persist for months perhaps because denervated vessels are sensitized to histamine (44) and other vasodilator metabolites.

After the initial intense hyperemia, moderately severe cases of immersion foot show a small rise or fall of temperature in response to immersion of the arms in hot or cold water The vasomotor disturbances of this group are similar to those described by Wilkins and Kolb (97) in cases of polyneuritis, and to those found by Richards (70) in cases of incomplete division of the sciatic nerve.

Such findings suggest that vasoconstrictor paralysis is an important factor in causing the continued hyperemia of immersion foot.

This hypothesis is further supported by the demonstration that the digital vessels are abnormally sensitive to circulating adrenaline and to the effects of local cold both those phenomena are known sequels of postganglionic sympathectomy (44,95)

Blue Color in Hyperemic Extremities In spite of the evidence of rapid blood flow the pink color of the hot feet is deeply tinged with blue With the limbs pendent, the depth of both colors increases rapidly on elevation, the feet immediately become blanched. What is the explanation for the blue color?

Three possible factors have been considered. In the first place it is likely that arteriovenous shunts are wide open and that there is an active deep circulation through damaged muscles. In this way the superficial skin capillaries and venules may be short-circuited so that the blood flow in them is reduced Secondly the increased temperature of the skin caused by the active deep circulation would increase its requirements for oxygen. Thirdly the blue color may mean nothing more than an increase in the amount of blood in the subpapillary venous plexus. Blueness in a highly colored skin does not necessarily indicate anoxia in polycythemia an increase in the amount of hemoglobin present at the surface causes an increase not only in redness but in blueness of the skin.

The Posthyperemic Stage and Cold-Sensitive States. The cold sensitivity of the late stages of immersion foot cannot be entirely explained by the recovery of tone in vessels remaining denervated Contributing factors are disuse (the increased muscle blood flow which accompanies even slight exercise and warms the overlying skin will not occur in denervated muscles) and the absence in denervated skin of the axon reflex (57,58) which is responsible for the local vasodilator reaction to cold and normally comes into play at temperatures below 15 to 18 C These and other factors in the causation of coldness following peripheral nerve lesions are discussed by Richards (69) and Doupe *et al* (28)

There remains the difficulty that coldness and cold-sensitivity persist in some cases of immersion foot where observations on sensation and sweating indicate that a large measure of nerve regeneration has occurred Here three further mechanisms may be involved

(*1*) Exposure to severe cold, whether dry or wet, sensitizes the peripheral blood vessels so that thereafter they are more susceptible to the effects of milder degrees of cold. The mechanism is obscure, but is presumably similar to that responsible for Raynaud s phenom-

enon. In the latter, the digital arteries are sensitized either as the result of repeated exposure to mild degrees of cold, or because of some inherent "local fault in the arteries themselves

(2) Intense vasoconstriction of sympathetic origin might account for persistent coldness of the extremities and failure of reflex vasodilatation. The presence of excess sweating is suggestive of increased sympathetic activity Reflex vasodilatation, however, may fail to occur even when initial temperature of the feet is fairly high (39) Failure of reflex vasodilatation or a gradual rise in temperature might be the result of occlusion of the main arteries This can be excluded in the majority of cases because the peripheral pulses are of good volume Patency of the arteries of the foot in one case has been demonstrated by arteriography (70) In histologic material, Blackwood (13) has failed to find occlusion of arteries except in areas immediately proximal to gangrenous tissue. The possibility that smaller vessels such as arterioles are occluded requires further consideration. In biopsies from cases of immersion foot 4 months after exposure, White and Warren (96) found extensive fibrosis of subcutaneous tissue and superficial muscle. They state

"The arterioles and venules show partial to almost complete occlusion as a result of a great increase of the fibrous tissue in their walls. The arteries and veins of larger caliber show the same type of fibrous thickening of the wall, but with a lesser degree of occlusion of the lumen."

If these findings are confirmed they would be quite sufficient to account for a failure of reflex vasodilatation. It may further be assumed that the constriction of nerve endings by interstitial tissue and collagen, which White and Warren suggest is the cause of the late pain in immersion foot, will affect vasoconstrictor nerves, thus interfering with normal vascular responses On the other hand, after failure of reflex vasodilatation there may be excellent response to the local injection of histamine (70) According to Lewis (57) this response is the result of an arteriolar dilatation.

(3) An alternative explanation has been put forward (87) Cold sensitivity is observed at a time when observations on sensation, sweating, and vasomotor responses suggest that a certain amount of regeneration of damaged nerve fibers has taken place. Partially reinnervated cutaneous blood vessels may behave like partially denervated vessels, and react excessively to chemical vasoconstric

tors (adrenaline, sympathin) circulating in the blood stream or produced locally

Sensitization of the skin vessels of the feet to circulating adrenaline can be demonstrated all through the hyperemic stage, at least after the first 10 days. During the adrenalinemia which accompanies insulin hypoglycemia, the temperature of the hot great toes falls steeply rising again as the symptoms pass off No such fall in temperature occurs in the normally innervated digits of the upper limb (Fig. 13) At other times, despite this sensitization to adrenaline, the feet remain hot presumably any vasoconstriction produced by the small amounts of adrenaline circulating under ordinary circumstances (in response to pain and emotion, for example) is insufficient to render the feet cold

With partial reinnervation, the situation is changed Now adrenaline (or a similar substance) is liberated at intact nerve endings, and this may diffuse and act upon portions of vessel which are still denervated. Such denervated portions of vessel being sensitized would respond with a stronger and more prolonged vasoconstriction than normally occurs. Denervated vessels are sensitized not only to adrenaline but to cold and the combined effects of cold and adrenaline are greater than their sum. This property of denervated vessels may be one factor in the cold-sensitive state

Against this theory is the fact that cold-sensitivity sometimes follows very mild immersion foot, and may persist long after there is any clinical evidence of denervation.

In conclusion, it may be stated that the available evidence favors the hypothesis that the initial hyperemia of immersion foot is the result of the release in chilled and partially ischemic tissues of relatively stable vasodilator substances once the effect of these has subsided, the hyperemia is maintained because there is a paralysis of peripheral vasoconstrictor nerve fibers. The late vascular phenomena are more difficult to explain, but it is assumed that they are the result of denervation and the subsequent reinnervation of peripheral blood vessels, which may also acquire a sensitivity to cold analogous to that seen in Raynaud's phenomenon.

DAMAGE TO THE SKIN BLISTERS AND GANGRENE

It has been suggested that the effects of cold are like those of a poison, and that the resulting damage is proportional to

Time (duration of exposure) × dose (intensity of cold)

This may be true within limits for the direct effects of cold on nerve or muscle, but separate consideration must be given to blisters and gangrene, which may be secondary to damage to the minute vessels.

The skin, being superficial is often blistered by a short freeze while biologically less resistant but deeper tissues escape serious damage. In immersion foot, however, if freezing can be excluded, blisters are of serious import, for they seldom occur except in cases with irreversible (degenerative) nerve lesions Indeed, prolonged immersion at temperatures insufficient to freeze the tissues may be followed by quite serious damage to nerves and muscles without any signs of skin damage apart from desquamation.

The same problem arises in respect to gangrene. A severe freeze may result in gangrene with very little nerve damage, except in areas within and closely adjacent to the necrotic area. The gangrene is not attributable to the direct effect of cold (which is seldom severe enough to cause irreversible changes in the skin) but to events consequent on thawing, which lead to "silting," stasis and ischemia.

The course of events has been demonstrated by Tannenberg, Ricker and others cited by Bigelow (9) by Rotnes and Krevberg (71), using diffusible and nondiffusible stains by Greene (46b) and by Lange and Boyd (55), who employed a fluorescein method. During exposure and for a variable time after thawing the arterioles in the injured area remain tightly constricted. In capillaroscopic studies Davis *et al* (26) found that capillary loops of the nail bed were not demonstrable for as long as 24 hours after high altitude frostbite.

The next stage of frostbite is characterized by maximum capillary dilatation and swelling. There may be a third stage when, apparently as a result of loss of plasma through the highly permeable vascular wall, the vessels become silted up with a sludge composed of red blood cells which conglutinate to a necrotic and homogeneous red column. At first the stasis is reversible, but if it persists for 72 hours the cell masses may become organized as true thrombi and gangrene ensues. In other cases a condition of prestasis is present any additional trauma, such as rubbing or undue warming, may tip the balance and produce complete stasis.

By *commencing heparin administration within 24 hours of the* freeze, Lange and Boyd (55) were able to prevent gangrene although motor and sensory paralyses persisted for several weeks Not all investigators are convinced of the value of heparin. Some claim good results from the use of plaster casts and pressure bandages, the object of which is to prevent excessive transudation and consequent stasis. Pressure of exudate is probably not an essential factor in tissue necrosis. The administration of heparin may prevent gangrene, even though the amount of swelling is considerably increased.

In immersion foot too gangrene may be due to silting and stasis. Parts which will become gangrenous blister extensively (4) and blistering at physiologic temperatures is a vital process. It would be confirmatory of the role of stasis if heparin prevented gangrene in injuries caused by chilling, but evidence on this point is not available.

Pathologic findings reviewed by Friedman (38) indicate that even *when frostbite is excluded thrombotic lesions are common in chilled* extremities damaged to the extent of gangrene Endangiitis obliterans was a feature of cold injuries sustained by German troops in Russia but, as Friedman suggests these injuries were probably sustained in freezing weather and endarteritis obliterans is a recognized sequel to frostbite Another difficulty is that many of the vascular lesions described by Siegmund Friedman and others may have been an *extension of inflammatory changes in infected extremities.*

Whatever its role in the causation of gangrene, thrombosis is certainly not an essential feature of injuries due to chilling. The most vulnerable tissues—nerve and muscle—may suffer extensive damage without any evidence of organic vascular occlusion either clinically or pathologically

DAMAGE TO NERVE AND MUSCLE

Nerves are readily damaged by freezing (27) but what evidence is there that cooling, short of freezing, will injure nerve tissue? Nerves in tissue culture can be preserved for weeks at 0 to 5 C Excised nerve for grafting is said to be unharmed by storage in a refrigerator but such nerve degenerates anyway and functions merely as *a tube for the downward growth of fresh axis-cylinders.*

began during the experiment, and sensory loss in the distribiuotn of the cutaneous branch of the musculocutaneous nerve took so long to recover that degeneration and regeneration presumably occurred.

Nicoll of the University of Indiana, showed me how hibernating bats stored in a refrigerator for 3 weeks and subsequently allowed to warm up flew away unharmed. The absence of any damage under such conditions may be related to the reduction of metabolism dur ing hibernation.

This brings us to the role of anoxia. Factors likely to give rise to anoxia during exposure include vasoconstriction, exudation of fluid impaired circulation due to pendency and immobility of the limb and deficient dissociation of oxyhemoglobin at low tempera tures Surprisingly little is known about oxygen requirements of mammalian nerve muscle and skin at these low temperatures Cold reduces metabolism, however and even without cooling limbs can withstand ischemia for several hours. It is of course possible that *spasm* of the vessels (including vasa nervorum) might persist for a time after rescue, but even so one can hardly attribute to anoxia the nerve damage which follows exposure for an hour or less as in the examples cited elsewhere in this paper Moreover although the neurologic findings in immersion foot bear some resemblance to those in ischemic conditions (see above) there are histologic differences between cooled nerves and nerves damaged by ischemia. In muscle too the histologic picture differs. The changes are patchy in distri bution and in their most severe form resemble Zenker's necrosis Blackwood and Russell (14) draw an analogy to the sweetening of potatoes by frost, and suggest that some tissue enzymes cease to work before others and that these metabolites may produce physico-chemical changes in muscle.

Thus, anoxia alone will not explain the damage to nerves and muscles. Cold is directly injurious in the intact warm blooded animal but apparently not in the hibernating animal or *in vitro* We conclude, therefore, that its damaging effect is in some way related to *tissue metabolism.*

Sensory Phenomena. Of considerable interest are the stabbing pains of immersion foot, which usually commence 7 to 10 days after rescue. Is this delayed onset related to the transience of a nerve block in the partially damaged pain fibers? Do such fibers "fire off" spontaneously? The onset corresponds fairly well with the appear

ance of end products of myelin degeneration. Is there any evidence that such end products are irritating?

Myelin is readily damaged and undergoes dissolution (27) Loss of myelin presumably involves loss of insulation of the axis-cylinder To account for the relief of causalgia by sympathectomy, Doupe postulates that impulses in efferent fibers cross over and stimulate adjacent partially damaged afferent fibers. The pains of immersion foot and trench foot, however are not relieved by sympathectomy

In respect to sensory loss, the volar surfaces of the hands and feet are affected earlier and to a greater extent than the dorsal surfaces. A similar distribution of sensory loss has been observed in polyneuropathies of nutritional origin and in ischemic limbs. Sir Thomas Lewis noticed that after the application of a tourniquet to the upper arm, the anesthesia spreads upward more rapidly on the palmar than on the dorsal surface of the hands

DISORDERS OF SWEATING

Although sweat glands in cooled skin may not entirely escape injury (38), the essential cause of the anhidrosis in immersion foot is interruption of sudomotor impulses in the peripheral nerves. As in other peripheral nerve injuries, anhidrosis corresponds in distribution to the area of sensory loss. Faradic stimulation fails to cause sweating once the nerves have had time to degenerate But the sweat response to injection of carbachol (a stable variant of acetyl choline) shows that the sweat glands are able to function.

During recovery sweating (mediated by fine, nonmedullated nerve fibers which regenerate and mature rapidly) returns rather earlier than awareness of touch and moderate pinprick. This was well shown in a sweat test carried out in one case (G7) 15 weeks after rescue (page 277) Although all parts of the toes were equally anesthetic, the only anhidrotic area was the zone supplied by the interdigital nerve removed at biopsy 2 weeks previously

Excess sweating begins at a time when there is partial recovery of sensation (with hyperpathia) and of vasomotor control (often with cold-sensitivity) This and the distribution of hyperhidrosis in marginal and previously anhidrotic areas, lead to the suggestion that partial reinnervation might be responsible (87) Like other effector organs in the autonomic nervous system, the sweat glands after denervation become sensitized to the chemical mediator. In this

case acetylcholine (22) The latent period before excess sweating begins may be related to the time needed for partial reinnervation of the sweat glands or for the recovery of partly damaged sudomotor nerve fibers. Once conductivity is restored to some fibers, acetyl choline is released at intact nerve endings, and diffuses to denervated sweat glands or portions of gland Such denervated structures, being sensitized, show an excessive and prolonged response. Efforts to test this hypothesis by pricking in graded doses of a stable variant of acetylcholine (acetyl beta methylcholine) were unsuccessful because the pricking alone was enough to provoke an outpouring of sweat.

As in causalgia, the hyperhidrosis is more readily elicited by pain or anxiety than by thermoregulatory stimuli Hyperhidrosis of the extremities is a feature of anxiety states, to which patients with chilled limbs are not immune. But this need not imply that hyperhidrosis in trench foot, for example is psychologic in origin, as some observers have suggested.

The hyperhidrosis cannot be due to the independent overactivity of the sweat glands, it is abolished at once by nerve block, and is effectively controlled by atropine which acts on the nerve endings (Fig. 5)

In an aviator with unilateral immersion hand (case RF1) the excess sweating was confined to the damaged extremity After 4 months, when motor and sensory defects had recovered and the hand was no longer cold sensitive, hyperhidrosis also ceased—perhaps because reinnervation was complete. In case B1 hyper hidrosis likewise passed off after a few months In most cases however hyperhidrosis (like cold-sensitivity) was still troublesome several years later despite more or less complete recovery in other respects. If incomplete reinnervation is the reason, the fault must lie either in the sympathetic nerve fibers or more probably in their junction with the effector organs (sweat gland and arteriole) Carefully planned biopsy studies might throw light on this problem. The type of fibrosis found by White and Warren (96) is perhaps not common, but changes much less gross than this would be sufficient to interfere with reinnervation.

Preventive Measures

Men abandoning ship are advised to take plenty of warm and waterproof clothing, loosely fitting boots, and extra socks in a watertight container

Efforts should be made to keep the bottom of the boat dry, or, if this is impossible, to raise the feet out of the water Ordinary footwear affords some protection during a short exposure, but, if the exposure is prolonged, swolling feet may be constricted and the circulation impaired A booted foot often sustains greater injury than a bare foot. Rubber boots have proved no better than leather ones, even if they do not fill with water they soon become wet inside from condensed perspiration. Whenever possible, wet socks should be wrung out or changed for dry ones, and if the boots feel tight they should be removed and not replaced Brownrigg (19) recommends the soft sealskin boots used by fishermen on the Grand Banks Cellular rubber boots provide considerable insulation, even against immersion in ice water (79) but it is still necessary to prevent the entrance of water from above. This could be attained by joining the boots to an immersion suit—say with rubber solution—to form a single watertight garment. Such a garment worn over ordinary clothing would protect body and limb against the chill of immersion and against cold, wind and wet while adrift.

Lewis and Love (61) have shown that a greasy skin supercools to a greater extent than a dry skin. Greasing the skin may lessen the risk of frostbite, but it cannot long delay the penetration of cold into limbs immersed in water Socks impregnated with vaseline have some insulating value (21)

In the early stages of exposure gentle rubbing is harmless and may help the peripheral circulation but massage will do harm once the skin is swollen, numb and friable The feet should be exercised and not kept pendent all the time. Tight clothing and cramped postures likely to interfere with the circulation are to be avoided

Treatment

Because therapeutic methods beneficial at one stage may be useless or even harmful at another the three stages of immersion foot will be considered separately

PREHYPEREMIC STAGE

When rescued the survivor must be carried and not allowed to walk on damaged feet. The first step is to warm the patient without

case acetylcholine (22) The latent period before excess sweating begins may be related to the time needed for partial reinnervation of the sweat glands or for the recovery of partly damaged sudomotor nerve fibers. Once conductivity is restored to some fibers, acetyl choline is released at intact nerve endings and diffuses to denervated sweat glands or portions of gland. Such denervated structures, being sensitized show an excessive and prolonged response Efforts to test this hypothesis by pricking in graded doses of a stable variant of acetylcholine (acetyl beta methylcholine) were unsuccessful because the pricking alone was enough to provoke an outpouring of sweat.

As in causalgia the hyperhidrosis is more readily elicited by pain or anxiety than by thermoregulatory stimuli. Hyperhidrosis of the extremities is a feature of anxiety states to which patients with chilled limbs are not immune But this need not imply that hyperhidrosis in trench foot, for example, is psychologic in origin, as some observers have suggested.

The hyperhidrosis cannot be due to the independent overactivity of the sweat glands It is abolished at once by nerve block, and is effectively controlled by atropine, which acts on the nerve endings (Fig. 5)

In an aviator with unilateral immersion hand (case RF1) the excess sweating was confined to the damaged extremity After 4 months, when motor and sensory defects had recovered and the hand was no longer cold-sensitive, hyperhidrosis also ceased—perhaps because reinnervation was complete. In case B1 hyper hidrosis likewise passed off after a few months. In most cases, however hyperhidrosis (like cold sensitivity) was still troublesome several years later, despite more or less complete recovery in other respects. If incomplete reinnervation is the reason, the fault must lie either in the sympathetic nerve fibers or more probably in their junction with the effector organs (sweat gland and arteriole) Carefully planned biopsy studies might throw light on this problem. The type of fibrosis found by White and Warren (96) is perhaps not common but changes much less gross than this would be sufficient to interfere with reinnervation.

Preventive Measures

Men abandoning ship are advised to take plenty of warm and waterproof clothing, loosely fitting boots, and extra socks in a watertight container

Efforts should be made to keep the bottom of the boat dry or, if this is impossible, to raise the feet out of the water Ordinary footwear affords some protection during a short exposure but, if the exposure is prolonged swelling feet may be constricted and the circulation impaired. A booted foot often sustains greater injury than a bare foot. Rubber boots have proved no better than leather ones even if they do not fill with water they soon become wet inside from condensed perspiration. Whenever possible, wet socks should be wrung out or changed for dry ones and if the boots feel tight they should be removed and not replaced. Brownrigg (19) recommends the soft sealskin boots used by fishermen on the Grand Banks. Cellular rubber boots provide considerable insulation, even against immersion in ice water (79) but it is still necessary to prevent the entrance of water from above This could be attained by joining the boots to an immersion suit—say, with rubber solution—to form a single watertight garment. Such a garment worn over ordinary clothing would protect body and limb against the chill of immersion and against cold wind and wet while adrift.

Lewis and Love (61) have shown that a greasy skin supercools to a greater extent than a dry skin. Greasing the skin may lessen the risk of frostbite, but it cannot long delay the penetration of cold into limbs immersed in water Socks impregnated with vaseline have some insulating value (21)

In the early stages of exposure, gentle rubbing is harmless and may help the peripheral circulation but massage will do harm once the skin is swollen, numb and friable. The feet should be exercised and not kept pendent all the time. Tight clothing and cramped postures likely to interfere with the circulation are to be avoided.

Treatment

Because therapeutic methods beneficial at one stage may be useless or even harmful at another the three stages of immersion foot will be considered separately

PREHYPEREMIC STAGE

When rescued, the survivor must be carried and not allowed to walk on damaged feet. The first step is to warm the patient without

directly heating his injured extremities. Stripped of wet clothing, the trunk and limbs are wrapped in blankets, leaving the feet uncovered. Hot drinks may be given and hot water bags placed near the trunk, but the patient should not be left near a fire.

The feet are exposed to the air and kept dry. Blisters and abrasions are treated with sulfonamide powder; dyes, such as acriflavine, stain the skin and obscure the color changes which need to be observed.

Until the circulation returns, the limbs should be kept horizontal since elevation may further diminish the blood supply. Oxygen by inhalation has been tried, but it might be more effective at this stage to surround the limb itself with oxygen.

Massage to the proximal parts of the limbs may be justifiable as an aid to restoring blood flow, but the fragile, edematous skin of the chilled extremities *must on no account be rubbed*.

Clinical and experimental observations for the most part confirm the age-old belief that warmth greater than that of the human body is harmful to frozen or chilled extremities. One patient, case ST6 (Fig. 11), had his feet baked under a radiant heat cage soon after rescue. Although the grade of vasoneuropathy was mild (right foot, grade B3; left foot, B4) the left great toe became gangrenous. There was, however, a history of old injury to the left leg, which may have affected the blood supply to this toe. Other patients, not in this series, also had their feet baked under heat cradles but were said to be none the worse. In some instances inquiry elicited that the feet were already hot when the cradles were applied.

The bulk of the evidence is against *strong* heating, but the question remains, should the chilled extremities be gently warmed, cooled, or left exposed to room temperature?

According to some workers, even gentle warmth is contraindicated because it increases exudation which in itself may be harmful (46,53,54,61,75). On the other hand, Brahdy (18) did not find that very slow thawing was important; many men with apparently severe frostbite went into warm rooms without bad effect. Certain Russian workers (40) have discarded the old method of gradual warming (rubbing with snow, etc.) of frozen tissues, and recommend instead rapid warming without overheating. Other investigators maintain that rapid rewarming in frostbite is impracticable because of the severe pain and swelling which result. On the Eastern Front,

diathermy was used by both sides, but mainly, it appears, in cases reaching base hospitals and presumably already in the hyperemic stage

Fausel and Hemphill (34) noted that local and general symptoms cleared much more rapidly in patients with immersion foot who took Finnish type steam baths than in others who were treated with bed rest and cooling. The authors did not state whether or not the condition was in the prehyperemic stage when the baths were taken.

A number of survivors from H.M.S *Glorious* had their feet dipped in warm water just after rescue (page 273) Although pain and swelling may have been unusually severe at the time, the degree of vasoneuropathy found subsequently was not consistently greater in cases so treated. Generally speaking, however individual variations in immersion foot have been too large to permit judgment of the end results of gentle warming on rescue.

In animal experiments Blackwood and Russell (14) found that gentle warming (water at 28 C and incubation at 37 C) increased the initial reaction, but made no difference to histologic findings a month later Heating up to 37 C. in hot air appeared to have a slightly adverse effect upon muscle recovery as determined histologically after a year (15)

Greene (46) recommends that from the beginning frostbitten or chilled extremities should be kept cold, in the region of 2 to 5 C Lewis (60) has shown that temperatures below 15 C are harmful to tissues. But Greene argues that temperatures of this order are optimal for the survival of isolated tissues in culture and of ischemic limbs, and that even gentle warming dangerously increases the metabolism of ischemic tissues increases exudation, and encourages the growth of bacteria warmth and bed rest, he maintains will check or abolish vasoconstriction. The circulation of adrenaline initiated in response to cold and emotional stress, as well as the reflex vasoconstrictor stimuli are reduced or inhibited by a change of environment, but cold has a powerful *local* effect, and arteries which are in spasm from the direct action of cold upon them are not likely to relax until they themselves are warmed. Thus keeping the extremities cold may have the unfortunate effect of prolonging the stage of vasospasm and ischemia.

Davis *et al.* (26) employed the treatment advocated by Greene for a series of patients with high altitude frostbite. They kept the

parts at approximately 2 to 5 C for 24 to 48 hours after injury had been sustained but although swelling and blistering were less the end results were rather worse than when the hands were allowed to warm up naturally to room temperature.

Inquiries have brought to light few records of immersion foot or trench foot strongly cooled in the prehyperemic stage, usually the feet were already hot when treatment was started. In some instances, hyperemia developed beneath the ice bags—"but not if they were properly packed." In several cases the onset of hyperemia was delayed 7 or 8 days, although pulsation was present in the dorsal pedal arteries.

Until we have more evidence as to the relative merits of methods so at variance as cooling to 2 to 5 C on the one hand and rapid warming to 37 C on the other an intermediate course seems advisable The degree of warmth applied should be no greater than needed to permit relaxation of the arteries exposure of the extremities to a cool atmosphere (18–22 C) appears to be a logical and in our experience, a satisfactory method The feet are protected by a cradle beneath which is placed a bath thermometer The environmental temperature in relation to the feet may be adjusted by altering the room temperature or if this is too low by covering the cradle with blankets and allowing warm air from beneath the bed clothes to enter at the proximal end.

Moderate warmth in still air will take a long time to penetrate severely chilled extremities. In cases treated by Channell aboard a destroyer feet exposed to still air at 12 to 15 C became hyperemic within 5 hours, but sometimes feet remain cold for as long as 2 days. At a suitable room temperature (18–22 C) warming might be hastened by the use of a fan which would have the additional advantage of checking hyperemia once it develops. Further experiments are needed before the optimum temperature for rewarming chilled extremities can be stated with certainty

Interruption of the sympathetic outflow by operation or infiltration has been recommended in the treatment of trench foot and frostbite by certain continental observers, but the findings of Lake (53,54) and Greene (46) suggest that the procedure is valueless and even harmful at this stage Davis *et al* (26) however claim that in high altitude frostbite blocking of the sympathetic trunk will effect dilatation of the peripheral capillary bed provided there has

been no permanent anatomic injury to the capillary wall or th
beds at the arteriolar capillary junctions In their experience
following drugs did not release vasoconstriction amyl ni
nitroglycerin, alcohol aspirin nicotinic acid, and mecholyl.

Any efforts to hasten the release of vasoconstriction, whethe
body warming, local warmth sympathetic infiltration, or drugs
do harm unless steps are taken to control the degree of vasodilat
when it occurs

HYPEREMIC STAGE

Lake (53,54), investigating methods of limiting the exce
exudation incurred during a too rapid return of the circula
found that he could diminish the exudation and consequent t
damage by tying the femoral arteries of animals. He also
vasoconstrictive drugs but was not impressed with the results.
frostbite in man, Lewis (60) recommends intermittent art
compression to allow blood to return gradually to the limb, w
is kept cool. Pressure dressings and plaster casts applied befor
swelling increases have been used in frostbite and trench foot
the evidence is conflicting. Treatment by cooling alone is
sufficient, and should begin as soon as vasodilatation develops.

According to Safford and Nathanson (72) the optimum cutar
temperature for prolonged therapeutic cooling is 70 F (21 C)
temperature may be maintained for hours or even days. V
hyperemia is intense ice bags may be used (92 93) Even ther
skin temperature may not fall below 80 F (26 6 C.), but pa
relieved and within a few hours the patient is more comfort
Edema usually subsides rapidly and blisters are resorbed. In
severe cases, too early removal of the ice bags is followe
refilling of blisters, increased edema, and even extravasation of b
Instead of ice bags, some form of cooling cabinet may be
(92 48 10 93)

Acknowledgments

Were it possible I should like to mention personally all those who helped in this work or so kindly gave information and advice I am particularly indebted to the Medical Director General of the Royal Navy who permitted this paper to be published. I am grateful, too for scientific hospitality received on a visit to the United States and Canada in 1945–1946.

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Blood Vessel Anastomosis by Means of a Nonsuture Vitallium Tube Method

Experimental Studies and Clinical Applications

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Introduction

The method of blood vessel anastomosis described in this paper and its possible clinical applications supplement the suture method of anastomosis popularized by Carrel (3). As will be stressed in detail later, the nonsuture method is not suggested for every case where vessels must be joined, but rather where there is a defect in the form of a gap in an artery or where two veins are being joined. Suture anastomosis may be preferable under certain circumstances, as we will attempt to point out.

References to the use of prostheses for arterial anastomosis date back to ancient times (9), but it was Payr (10) who in 1900 described a method of passing one cut end of an artery through a magnesium ring, everting it, and then passing the other cut end of the artery over the ring and holding it in place with a ligature, thereby providing a contact of intima to intima. Höpfner (5), in 1903, performed extensive experiments with Payr's method and, in addition, attempted ten vein grafts to bridge arterial defects in dogs. In each instance there was complete failure, and he concluded that the vein graft method should never be employed. To our knowledge there is

no report in the literature of a successful vein graft anastomosis employing prostheses, either clinically or experimentally until 1942 (1) when by means of the nonirritating vitallium tubes and a broad intima to intima contact we obtained uniformly satisfactory vein graft anastomoses of a dog's femoral arteries. Höpfner's modifications of Payr's method failed for two basic reasons (1) Highly irritating magnesium tubes were used (2) The holding ligature, i.e., tissue strangulating ligature was placed within 2 mm. of the end of the tube thereby allowing an overlap of only a 1 mm of artery and vein graft for healing purposes.

The nonsuture method is unnecessary when the cut ends of an artery can be approximated without undue tension suturing is then entirely adequate However in most instances a gap in the artery must be bridged and a vein graft has to be employed Under such conditions the nonsuture vitallium tube method is entirely satisfactory and has been highly successful in our hands clinically as well as experimentally

Technic

Vitallium an alloy * was selected as a suitable material from which to make cannulas or tubes because this metal may be left in tissues for indefinite periods without causing objectionable irritation. To facilitate bridging arterial defects of any length we recommend an identical technic employing a vitallium tube on each end of the vein graft.

Figure 1 *illustrates the technic The ends of the vein graft are* everted (cuffed) over the ends of the cannula or tubes and secured by fine silk ligatures placed behind tying ridges 4 or more mm. from the ends of the cannula or tubes The cut ends of the artery are then brought *over the vein-covered ends of the canula or tubes,* and secured by heavy silk ligature placed behind the tying ridges. To prevent the penetration of blood between the intimas of vein and artery a fine silk ligature is tied just snug, 1 or 2 mm. from the end

The method affords a broad contact of vein intima to artery intima for healing since the holding ligature is well away from the flowing

* Vitallium is composed approximately of 65 per cent cobalt 30 per cent chromium, and 5 per cent molybdenum. The tubes were supplied by Austenal Laboratories, Inc Chicago, New York

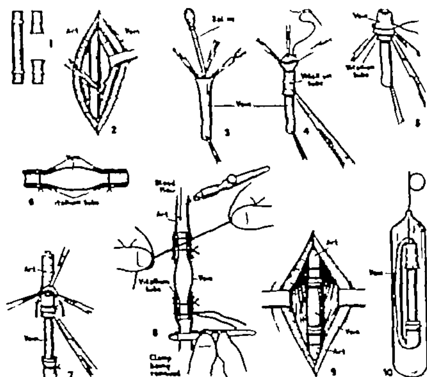


Fig. 1 Operative technic of the nonsuture method (1b) 1 Cannula and tubes (for use in the one-tube or two-tube technics) 2 Removal of vein graft note that the branch is tied close to the vein with fine silk before clamping 3, Irrigation of vein graft with isotonic sodium chloride solution, to which a small amount of heparin may be added if desired. 4 Triangulation of end of vein with mosquito clamps 5 Cuffing and securing everted end of vein on vitallium tube 6, Two-tube technic with vein graft mounted. 7 Introducing distal end of vein graft mounted on vitallium tube into proximal end of artery 8 Tying fine silk ligatures, just snug, to prevent blood from penetrating between the intimas of vein and artery also, releasing the proximal rubber-shod clamp first to facilitate distalward passage of any residual air bubbles within the graft 9 Completed anastomosis when possible perivascular tissues are closed snugly around anastomosed artery 10 Convenient method for preserving a vein graft for quick-freezing, hermetically sealed in an ordinary test tube The graft is moistened with isotonic sodium chloride solution one end is mounted on a vitallium tube in the usual manner the other end is passed through a second tube and brought over the first tube to protect the intima until the graft is used A wire serves to suspend the graft

blood In the presence of bacterial contamination this type of junction would seem to offer an advantage over the suture junction, for in the latter the vessel wall encompassed in the suture line, and thereby somewhat strangulated, lies in direct contact with the flowing blood. Furthermore, the joint is leakproof in the presence of anticoagulant therapy On the other hand because of blood to intima contact only, the anastomosis affords little or no stimulus to thrombus initiation when the blood clotting time is normal.

Certain technical facts became clear during the development of the method These are based on principles well known to surgeons, and fortunately have in no way affected the simplicity of the procedure They are

(1) Length of Vein Segment One should avoid exceeding physiologic longitudinal tension on the anastomosis and by the same token avoid redundancy and angulation of the vein graft. Roughly 2 cm. is allowed for cuffing the ends of the vein on the vitallium tubes. The arterial defect is estimated allowing for debridement of the severed ends by bringing the ends of the artery toward each other at estimated physiologic tension. To this estimate 2 or 3 cm. are added, to indicate the proper length of the vein segment before removal The same rule applies to choosing the length of preserved vein grafts, when stretched to approximate physiologic tension

(2) Crushing Clamps on Vessels Their use should be avoided In preparing the vein graft, the branches should be ligated with B Deknatel silk almost flush with the vein, the branch is then clamped distally and cut (Fig 1 2) To remove the vein graft, first ligate distally (empty the vein of blood) then proximally with a noncrushing ligature quickly remove the graft, irrigate and place it in saline solution. The stumps of the vein remaining in the body are then further secured by means of transfixion ligatures.

(3) Choice of Vitallium Tubes Do not make the procedure difficult by selecting tubes too large for the artery Choose tubes slightly but definitely smaller than the distended state of the proximal end of the artery and if the arterial defect is great, use an even smaller tube distally

(4) Mounting of Tubes on Vein Graft The ends of the vein graft are pushed through the vitallium tubes everted (cuffed) over the ends (care being taken to avoid a valve site) and held by no. 0 Dek

(8) *Release of Clamps* Release proximal rubber-shod clamp first allow the graft to fill with blood and immediately release the distal clamp permitting the blood to pass on This procedure generally forces any air bubbles on beyond the graft—an important point. Gentle compression of the graft together with elevation of the extremity will insure passage of any air bubbles trapped in the graft

(9) *Debridement* The vein graft anastomosis should in no way be permitted to interfere with adequate debridement. The ends of the arteries properly secured to the vitallium tubes with double ligatures permit gentle displacement of the graft for debridement or for completing a debridement previously begun. No attempt should be made to approximate perivascular tissues which may be under tension over the vein graft. In many instances the perivascular tissues will adequately cover at least the vitallium tubes The average vein graft will do well even if exposed.

Experimental Observations

Employing no anticoagulants and using the silk technic throughout, the small femoral arteries of dogs were selected for testing the efficiency of the nonsuture method The reasons for this choice were (1) Abundant experience has shown that suture anastomosis of the femoral arteries of dogs with or without the use of vein grafts fails as often as it succeeds even when undertaken by skilled operators under rigid aseptic precautions whereas the same technic may be employed to anastomose the aorta or carotid with fairly regular success (2) A review of the literature on methods employing a nonsuture prosthesis for the anastomosis of blood vessels reveals not a single successful instance of bridging defects of the femoral artery in dogs by the use of vein grafts

With careful attention to details of technic and asepsis and by using a generous segment of femoral vein from the opposite leg our nonsuture method affords a 90 per cent expectance of success in bridging defects of the small femoral arteries of dogs and without the use of anticoagulants.

We have explored anastomoses of the small femoral arteries of dogs up to 69 days after operation and found them patent Figure 2 is a photomicrograph of the artery vein junction following removal of the cannula in a one tube vein graft anastomosis patent 35 days after operation Note the excellent healing at the artery vein junc

tion. The vein graft appeared healthy and well nourished throughout. This is of interest for the vein graft in the one tube technic lies within the vitallium cannula entirely isolated from the perivascular tissues.

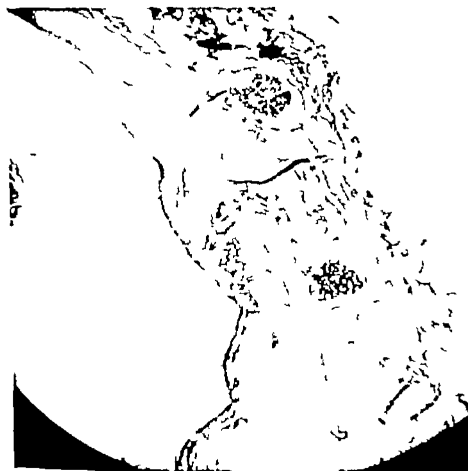


Fig 2 Section of specimen removed from animal (dog 1550) showing the junction of artery and vein which has been bridged by intima (1a)

The method was used to anastomose the abdominal aortas of dogs using external jugular vein grafts and the two-tube technic with regular success. 3 animals were observed for a period of eight months. On exploration the anastomoses were patent and the vein grafts were not dilated. The walls were somewhat thickened and had every appearance of being healthy.

ANASTOMOSIS OF BLOOD VESSELS IN CONTAMINATED WOUNDS

Because of widespread bacterial contamination in the case of accidental vascular injuries it seemed important to study the efficiency of the nonsuture method using the double-tube technic in contaminated wounds and comparing it with the Carrel suture method of anastomosing arteries.

Technic. Delayed anastomoses of femoral arteries in dogs were made through dirty open wounds 6 and 24 hours after unsterile ligation and section The arterial defects were bridged with free femoral vein transplants No anticoagulants were employed

The study embraced 5 series of animals affording an observation of 10 to 20 anastomoses in each series. In all series 1.5 Gm sulfanilamide was placed in alternate wounds In 2 series—one Carrel suture and one nonsuture—1 Gm. sulfathiazole was given by mouth twice daily The wounds in one Carrel suture and one nonsuture series were irrigated with saline solution, whereas in the remaining 3 series *careful debridement of the wounds was carried out at the time the anastomoses were performed*

Results. The success of the Carrel suture technic was boosted from 10 per cent to 40 per cent by the debridement and the use of sulfonamides. In general however the study confirms what has long been known namely the low efficiency of the suture method of anastomosing blood vessels in contaminated wounds Cultures taken *at the sites of failure (thrombus site of secondary hemorrhage and aneurysm)* invariably revealed bacterial growth (Fig 3)

The interesting results with the use of the double-tube nonsuture method in 24 hour delayed anastomosis of femoral arteries in contaminated wounds invited analysis and comparison with the entire group In the first place anastomosis of arteries in contaminated wounds offers a sensitive index of the bacterial status and the relative efficacy of measures for the control of infection For example, comparing results of anastomoses in the 6 hour contaminated wounds with the 24 hour wounds in which bacterial invasion has begun, a "fall-off" of 25 per cent in successful results occurred in the latter in spite of debridement of the 24 hour wounds versus simple irrigation in the 6 hour wounds As for debridement, of the 13 delayed anastomoses receiving sulfanilamide locally but without debridement, there were 13 failures (100 per cent) whereas in 24 hour delayed nonsuture anastomoses success followed debridement alone in 30

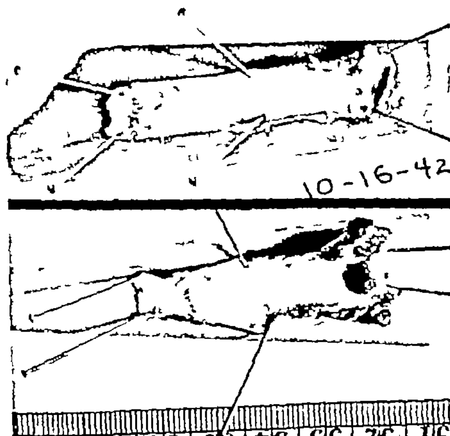


Fig. 3 Specimens showing aneurysms at the sites of anastomoses (1a) Note the aneurysms in the upper right of animal No 1937 and the lower right of animal No 2018. The latter one is almost completely filled with thrombus.

per cent of the cases Debridement plus oral administration of sulfa thiazole raised the successful results to 60 per cent addition of sulfanilamide in the wounds raised the successes another 15 per cent These findings were in accord with war experience which was that debridement greatly enhances the effectiveness of sulfonamides in contaminated wounds

In these delayed anastomoses in contaminated wounds it was interesting to observe that secondary hemorrhage occurred only once following the nonsuture technic and this in a 24 hour wound without the use of sulfonamides We have never observed an aneurysm at the artery vein junction or in the vein graft.

HETEROPLASTIC VEIN GRAFTS

At the suggestion of Dr Rudolph Matas, we thoroughly investigated the usefulness of heteroplastic vein grafts and means of preserving them. We have satisfied ourselves beyond doubt that the extremity will be saved if an anastomosed artery can be kept patent up to 14 days, i e beyond the period of posttraumatic edema by that time collateral vessels will have developed sufficiently to avoid the occurrence of gangrene. There is an abundance of evidence clinical as well as experimental in support of this opinion.



Fig 4 Appearance of dog 2110 (12 days postoperatively) and dog 2002 (21 days postoperatively) (la) The right hind leg of each had been amputated at midthigh level and re-implanted after being kept in cracked ice for 21 hours. Moderate edema is still present in dog 2110

To gain information on whether heteroplastic veins will function adequately to prevent gangrene when used to bridge arterial defects the right hind legs of 2 dogs were amputated at midthigh level (Fig. 4) After an interval of 24 hours the legs were reimplanted the nonsuture two-tube technic being used and vein grafts from a third and fourth animal to bridge the defects in the femoral artery and vein The amputated limbs were preserved during the 24 hour

interval in cracked ice The dogs were given 1 Gm. of sulfathiazole twice daily by mouth from the time of the first operation The photographs were made 12 and 21 days respectively after reimplantation of the limbs there was every evidence of a good supply of arterial blood in these reimplanted legs

The survival of the legs in the 2 dogs depended solely on the function of vein segments transplanted from other dogs and in this sense the experiments are critical. However we have used heteroplastic vein grafts to bridge femoral artery defects in 10 additional dogs The anastomoses function for an average of 27 days which is well beyond the postulated 14 days of posttraumatic edema

Figure 5 is a photograph of a dog's aorta in which a defect has been bridged with a segment of human saphenous vein by the non suture method using two 7 mm vitallium tubes The photograph was taken at exploration 19 days after the anastomosis had been performed Pulsation in the femoral arteries had remained excellent The vein graft was patent and without evidence of beginning thrombus formation nor was there any evidence in its gross appearance to indicate that resorption had begun.

PRESERVATION OF VEIN GRAFTS

Any method of preserving veins so that they will function successfully when used subsequently as grafts to bridge blood vessel defects must meet a number of rigid requirements Not only must the intima be preserved in a normal state in order to prevent thrombus formation initiation at the first onrush of blood when the anastomosis is completed but the mechanism must be intact so that the normal physiology of the part can be immediately resumed. And finally the method must take care of a varying degree of bacterial contamination of the veins at the time of their removal. (Veins removed according to the usual aseptic technic will reveal bacterial growth on culture in 3 out of 4 instances.)

We have found that veins which are quick frozen in an alcohol—solidified carbon dioxide mixture and kept in the frozen state will function adequately when used as heteroplastic grafts to bridge arterial defects and without the use of anticoagulants As a matter of fact the segment of human saphenous vein used to bridge a defect in the dog's aorta (Fig 5) was kept for 24 hours in the ice box and then quick frozen and preserved for 3 weeks before using. Appar



Fig. 5. Dog's aorta, 19 days after operation in which a defect had been bridged with a segment of human saphenous vein by the nonsuture method (1b) using two 7 mm. vitallium tubes. Vein graft can be seen between the exposed funnel ends of the tubes.

ently veins may be kept frozen for indefinite period For example on September 8 1943 defects in the right and left femoral arteries of dog 2283 were bridged with segments of femoral veins from dog 2219 preserved quick frozen since June 16 1943 (nearly 3 months) The nonsuture method of anastomosis was employed using two 3 mm. vitallium tubes with each artery and without the use of anti coagulants On September 22 (2 weeks after the anastomoses had been performed) both vein segments were exposed and proved patent. The wounds were left open to heal by granulation On October 16 (38 days after the ana tomoses) the wounds were re explored. The vein grafts were patent and the anastomoses func tioning. There was no evidence in gro appearance of beginning resorp ion of the heteroplastic grafts

Illustration 10 in Figure 1 shows a conv nient way of preserving a vein graft quick frozen for emergency use for instance to bridge a defect in the carotid artery should evidence of cerebral damage begin to appear Note that one end of the vein graft is already cuffed on one vitallium tube with the other brought over it to protect the intima. Care should be exercised not to exceed physiologic tension in selecting the length of the graft used to bridge a given arterial defect of equal importance is avoidance of redundancy

We have repeatedly been able to demonstrate that with ready mounted vein grafts at hand, the anastomosis may be completed within 15 minutes

Clinical Applications

Acute Traumatic Blood Vessel Damage

Trauma to an artery as a result of street accidents bullet and knife wounds and football injuries (such as posterior dislocation of the knee) usually causes a loss of substance in the vessel with retraction of the ends so that a gap must be bridged if blood flow through the vessel is to be restored The nonsuture method is ideal for this purpose when operation is possible within 12 hours If no gap exists as in a lateral laceration of the artery then suturing with 5-0 Deknatel silk on an atraumatic needle is entirely satisfactory No matter which method is employed heparinization is of the utmost importance it should be maintained by the immediate injection of 10 to 20 mg. of heparin intravenously at the completion of the anastomosis followed by subcutaneous injection of 100 to 200 mg

of heparin in Pitkin's menstruum* at the end of the operation. Heparinization is carried out for 3 to 5 days with the clotting time between 15 and 30 minutes

Case 1 *History* M E., a 7 year old boy was admitted to Presbyterian Hospital on July 20 1943 in shock due to hemorrhage from a severed brachial artery The boy's left arm had been pushed through a glass door while at play He received an irregular laceration across the inner aspect of the middle section of the arm The brachial artery and the median and ulnar nerves were severed The patient was promptly given 500 cc of blood 300 cc of isotonic solution of sodium chloride and 2 Gm. of sodium sulfadiazine intravenously

Operation Five hours after injury under ether anesthesia a pneumatic tourniquet was applied well above the wound The skin was carefully prepared and the wound was thoroughly irrigated with saline solution The retracted ends of the severed brachial artery were freed for a distance of 5 to 6 cm. The tourniquet was released sufficiently to flush out severed vessels. Rubber-shod clamps were quickly applied to the ends of the severed artery and it was irrigated with saline. The cut ends of the brachial vein were transfixed with C Deknatel silk. As debridement proceeded the smaller vessels were ligated with B Deknatel silk.

At this point of the operation the team was divided one section proceeded with repair of the nerves using arterial silk while the other proceeded with preparation of a vein graft for bridging the arterial defect The left femoral vein was isolated for a distance of 10 cm distal to the origin of the profunda femoris Branches were ligated with 0000 Deknatel silk flush with the vein clamped cut, and ligated distally (Fig. 1) A ligature of 000 Deknatel silk was placed on the distal end of the femoral vein The blood was milked upward and another ligature placed proximalward The vein was further secured with transfixion ligatures and the intervening segment was quickly removed (The length of a vein segment before removal should be 2 cm longer than the arterial defect.) The vein graft was thoroughly irrigated with saline A silk suture on a straight needle passed through the wall of the distal end served to pull the vein through a 2 mm vitallium tube and later when cut

* Manufactured by William R. Warner & Co 113 W 18th St., New York.

short to identify the distal end of the vein graft. The end of the vein was everted (cuffed) over the vitallium tube and held in place by a ligature of no 0000 Deknatel silk placed behind a tying (holding) ridge (Fig. 1) The other end of the vein graft was mounted in identical manner on a second 2 mm. vitallium tube (Care must be taken to avoid a valve at the eversion to prevent diaphragm occlusion.)

Next the severed end of the artery were debrided and again irrigated to remove clinging particles of fibrin. (Blood flow must be absolutely controlled by the rubber-shod clamps placed well away from the ends)

The distal end of the severed artery was then triangulated by placing mosquito clamps taking 1.5 mm. bites on the cut edge The flange of the vitallium tube carrying the proximal end of the vein graft was grasped with a stout straight clamp and the graft was dipped in saline. Following this the vein-covered tube was introduced into the funneled end of the artery and the latter was brought well up on the tube. The artery was secured to the tube intima to vein intima, by a no 0 Deknatel silk ligature tied tightly behind the holding ridge, using a surgeon s knot (Fig 1)

The second vitallium tube bearing the distal end of the vein graft was irrigated with saline (using a blunt nosed medicine dropper) and quickly introduced into the proximal end of the artery as above. Finally ligatures of 000 Deknatel silk were placed around the artery at a point 1 to 1.5 mm. from the ends of the vitallium tubes and tied just snug (Fig. 1)

Just before removing the rubber shod clamps 15 mg. of heparin was injected in the artery immediately proximal to the anastomosis using a hypodermic needle The proximal clamp was removed first followed immediately by removal of the distal clamp (Should this be ineffective in forcing all trapped air bubbles distally from the vein graft elevation of the limb with gentle milking pressure on the graft must be restored to)

A pink color in the boy s hand was the immediate result after reestablishment of blood flow and only a few minutes elapsed before the left hand was as warm as the right The muscles fascia and skin were approximated with fine silk. The patient received 300 cc of blood during the operation and left the table in excellent condition. The arm was placed in a plaster splint with the hand in volar flexion.

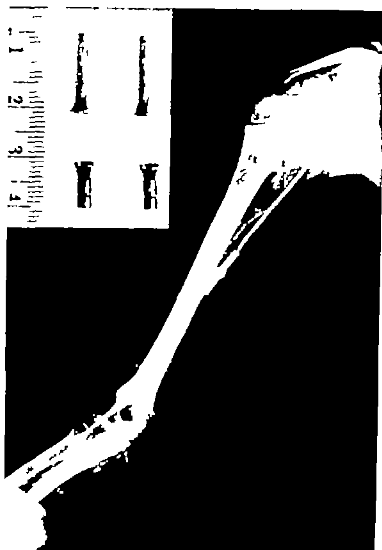


Fig 6 Arteriogram of the anastomosed brachial artery 1 month post operatively (1b) The funneled end of the vitallium tubes are close together and a column of diodrast may be seen passing through the intervening vein graft. Compare the long tubes used in this case with the recently designed shorter tubes shown in the inset.

Postoperative Course The wound healed by first intention The patient was discharged on the eleventh postoperative day in a con stant tension splint, which permitted exercise of unopposed extensor

muscles but protected the paralyzed flexor muscles of the forearm against overstretching. Sulfadiazine therapy was continued through the fifth postoperative day. We cannot say that postoperative heparinization was adequate (its administration by continuous drip was discontinued after 60 hours) because the clotting time (capillary method) varied from 3 to 6 minutes. Daily observations of the left radial pulse revealed it to be unchanged in volume.

Follow Up. At 1 month postoperatively patient was receiving physical therapy. The left radial pulse remained good. An arteriogram (Fig. 6) confirmed the patency of the anastomosis. However thrombosis of the anastomosis immediately followed the injection of the diodrast.

At 5 months chronaxia studies revealed innervation of the forearm muscles supplied by the median nerve.

At 14 months there was complete sensory and motor recovery of the median and ulnar nerves. Some inability to extend the fingers completely remained due to weakness of the interosseous muscles although chronaxia studies revealed complete regeneration.

At 17 months there was complete return of function.

Case 2. *History.* R. J., a 15 year old colored boy, entered Presbyterian Hospital on July 7, 1944 with a severe laceration of the left arm which he incurred in falling through a plate glass window. A tourniquet was promptly applied at the time of injury. After arrival at the hospital some hours later a pneumatic tourniquet was applied, and deflated at 1/2 hour intervals. Family and past history were noncontributory. His temperature was 101 F., pulse 132, blood pressure 160/80. He presented the picture of an apprehensive well-developed boy who was not in shock. Examination of the left arm revealed a transverse laceration starting in the mid biceps region, directed obliquely downward, dividing all soft parts to the bone and entering the elbow joint anteriorly. The laceration involved approximately two-thirds of the circumference of the arm. The radial and median nerves were severed as were the brachial artery and accompanying veins. As a result of muscle retraction, the wound gaped widely. The forearm and hand remained cold, pale, and pulseless following release of the tourniquet (Fig. 7A–B).

Operation. The wound was debrided. The nerves were sutured with fine silk. The brachial artery defect was bridged with a segment of great saphenous vein, using two 4 mm. vitallium tubes. The wound was closed primarily.

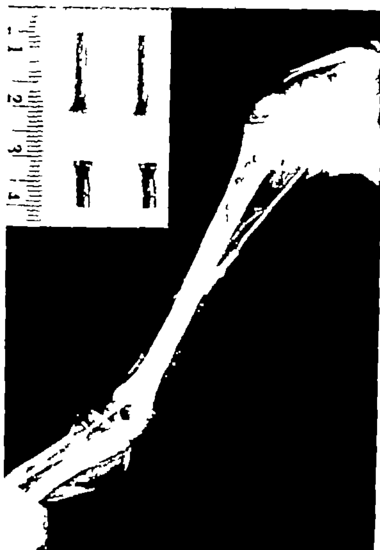


Fig. 6. Arteriogram of the anastomosed brachial artery 1 month postoperatively (1b). The funneled ends of the vitallium tubes are close together and a column of diodrast may be seen passing through the intervening vein graft. Compare the long tubes used in this case with the recently designed shorter tubes shown in the inset.

Postoperative Course. The wound healed by first intention. The patient was discharged on the eleventh postoperative day in a constant tension splint, which permitted exercise of unopposed extensor



Fig. 7A. Severe laceration of left arm—lateral view of wound (Ib)

Fig. 7B Severe laceration of left arm—anterior view of wound (Ib)

At 2 years there was excellent function of the vein graft, as indicated by pulsation of the vein graft and a strong radial pulse. There has been considerable improvement of forearm muscles but flexion of fingers remains incomplete

Management of Acute Arterial Injury The following procedures are of value prior to the definitive operative procedure

(*1*) Immediate control of hemorrhage If a tourniquet is necessary as it probably is it should be broad and well padded A blood pressure cuff is ideal because of the ease with which it can be inflated and released at ½ hour intervals

(*2*) Treatment for shock. Whole blood transfusions are best in these cases since these promote the maximum oxygen-carrying capacity of the circulating blood

(*3*) Control of pain and vasospasm The best single drug for this purpose is 1 grain (0 06 Gm) of papaverine hydrochloride intravenously followed at 2 hour intervals with ½ grain (0 03 Gm.) subcutaneously Frequent administration of alcohol in the form of whiskey gives excellent results

(*4*) Chemotherapy Penicillin is undoubtedly the agent to be preferred in these cases From 30 000 to 50,000 units should be given intramuscularly followed by injections of 20,000 to 25,000 units at 3 hour intervals Second best are the sulfonamides but a high blood level should be attained as rapidly as possible The patient should of course be protected against tetanus

(*5*) Preservation of a lowered temperature in the wounded extremity It is now recognized that maintenance of a lowered temperature reduces the metabolic rate in anemic tissues and is an important factor in delaying the onset of irreversible changes Usually it is not difficult to attain the right degree of chilling. It is well to remember that a completely anemic extremity will quickly assume the temperature of the ambient air If the latter is below freezing the limb must of course be covered sufficiently If on the other hand the ambient air is above 50 or 60 F the limb may be chilled by swathing it in moist bandages* and directing on it a current of air during transport or by an electric fan. And finally ice bags may be used but guardedly for example for ½ hour period with 15 minute intervals between

(*6*) Position of limb When at rest or in transport the limb should

* In our experience wetting the gauze with alcohol at ½ hour intervals is a simple way to chill a limb.

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be so placed that it i 4 to 6 inches below the heart level Thi sufficiently elevates the venous pres ure in the extremity to keep the little blood that may arrive via the collateral circulation long enough for complete deoxygenization

Delayed Treatment of Blood Ves el Injuries

The non uture method i recommended in the delayed treatment of traumatic arterial aneurysm an l arteriovenous fi tulas—some 6 weeks to 2 month or more after injury

We present a case to illu trate the u e of the non uture method to restore blood flow in the artery after exci ion of an arteriovenous fistula.

Case 3 *History* J W a 24 year old man entered Presbyterian Hospital on July 25 1944 complaining of a pulsating swelling of the right thigh of $2\frac{1}{2}$ years duration Pa t hi tory and family hi tory were noncontributory The pul ating tumor became apparent to the patient a few days after he had su tained a bullet wound His main complaints were increased sen itiveness of the leg to cold decreased exercise tolerance both in the leg and generally and exertional dyspnea. On physical examination the heart was enlarged, and a systolic murmur was heard over the precordium Blood pressure in the right arm was 110/40 Examination of the right leg revealed a pul ating ma s 5 by 3 cm over Hunter s canal at the junction of the upper and middle thirds of the thigh. A small scar in the overlying skin marked the entrance of the bullet A thrill was palpable over the mass and a continuou bruit with systolic accentuation could be heard Pulsation was faint in the right popliteal artery and absent in the distal arteries Obstruction of blood flow through the fistula caused pronounced bradycardia Roentgenography revealed an increase in the transverse diameter of the heart most pronounced to the left Hemoglobin was 14.8 Gm. red blood cells 5,910,000

Operation This consisted of excision of the arteriovenous fistula with vein graft bridging of the arterial defect by the nonsuture method using a segment of the accompanying femoral vein The fistula measured approximately 1 cm. in diameter Pressure closure of the fistula caused an increase (from 4 to 8 mm.) in the diameter of the distal portion of the femoral artery The diameter of the artery proximal to the fistula was approximately 12 mm., with some thinning of the vessel wall On release of the rubber-shod clamps and



Fig. 9 Diodrast visualization of arteriovenous fistula before operative excision of the fistula (1b). Note the spasmodic narrowing of the artery proximal to the fistula site, and its dilation at the site. A segment of the hugely dilated vein was used as a graft to bridge the arterial defect after the fistula was excised.

re-establishment of the circulation, the vein graft dilated to 2 cm. this was considerably reduced by closing the perivascular tissue snugly around it. Following the anastomosis, there were excellent

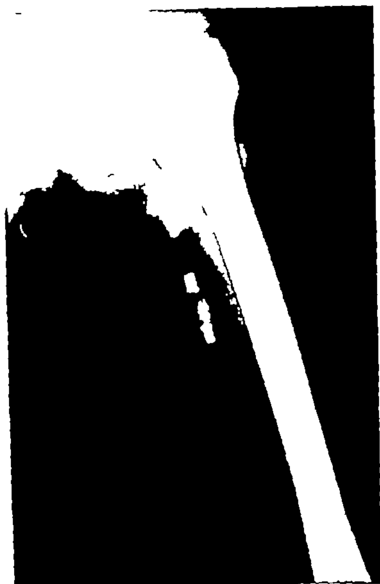


Fig. 10 Arteriogram 14 days after operation, demonstrating the patency of the anastomosis (Ib) Note the small size of intervening vein graft as compared with Figure 9

pulsations in the dorsalis pedis and posterior tibial arteries Two weeks later patency of the anastomosis (Figs 9 and 10) was confirmed by arteriography Blood clotting time was maintained around 30 minutes for 8 days following operation, by means of subcutaneous administration of heparin

Circulation studies done before and after operation with the patient at rest, using the radioactive isotope of sodium gave the following results (*1*) Circulation time (arm to foot) of the normal left leg was 40 seconds compared to 30 seconds for the right leg after operation. (*2*) Volume flow to the right foot preoperatively was 40 per cent below the normal left foot postoperatively volume flow to the right foot increased to 20 per cent above the normal left leg.

Follow-Up At 5 months after operation examination revealed equal pulsation of the leg arteries on palpation but with slightly higher oscillometric readings on the right (affected) leg. The patient goes on 10 mile deer hunts walking up and down mountains without the slightest evidence of diminished exercise tolerance

At 17 months postoperatively the patient was winning tennis matches and skating races. The preoperative sensitivity of the leg to cold has disappeared

It is an established fact that quadruple ligation with excision of the fistula eliminates the likelihood of recurrence in cases of traumatic arteriovenous fistula Furthermore there is little likelihood that gangrene will follow this procedure when it is done 2 or more months after injury All concede that the procedure eliminates the deleterious effects which this disease has on the heart. Nevertheless, although the patient may show great symptomatic improvement after this operation only rarely is the affected extremity capable of as full exertional response as the normal extremity without the occurrence of some symptoms

Three cases of traumatic arteriovenous fistula of the femoral vessels treated by ligation with excision of the fistula were followed up The findings were as follows One man 26 years old reported discomfort in the calf of the leg when walking 2 years after operation A 29 year old man 4 years after operation can only walk 2 miles at a slow pace without developing leg fatigue and pain he was discharged from the Army for this reason. The third patient, a 30 year old professional dancer has not been able to resume his work because of leg symptoms now 5 years after operation. None of the 3 patients have been able to indulge in the vigorous sports or exercise to which they had been accustomed before the injury To compare with these results there is a case of arteriovenous fistula of the popliteal vessels on which one of us (A H B) operated in 1934 Patency of the parent vessels was successfully maintained with elimination of the fistula

by recon tructive aneurysmorrhaphy The young man took up professional boxing after the operation and ha carried on with vigorous exercise remaining completely free of symptoms Now 8 years after operation there i equal pul ation of the arteries in both feet There wa no section of sympathetic nerves at operation

It would seem worth while therefore to maintain patency of the parent artery particularly in cases of arteriovenous fistula of the leg. We believe that vein graft bridging u ing the nonsuture technic will make this fea ible in a large percentage of cases Such a procedure affords a chance for complete restitution of function under all exercise condition —a particularly important fact when the patient is a young man In the ca e described above the young man s greatest ambition wa to regain hi laurel a an amateur skater

Pathologic Peripheral Arterial Aneurysms

More than 30 years ago Dr Rudolph Mata demonstrated a curative operative procedure for peripheral aneurysm which embraced the all important feature of preserving the collateral blood vessels in an undamaged state Hi operations—obliterative restorative and recon tructive endo-aneurysmorrhaphy—are known the world over In hi great experience he has attained the ideal in a considerable number of cases namely cure of the aneurysm with pa ency of the parent artery maintained However comparatively few peripheral aneurysm are suitable for the restorative or reconstruc ive operation

When peripheral aneurysm at operation appear unsuitable for the Matas restorative or reconstructive endo-aneurysmorrhaphy but at the same time present some good reason for maintaining the patency of the main extremity artery the nonsuture method may be employed a follows (Fig. 11) The parent artery is exposed immedi ately proximal and distal to the sac A double turn of umbilical tape or rubber-shod clamps are then placed about the artery to control the blood flow Less immediate blood loss will occur if before opening the aneurysmal sac a pneumatic tourniquet is placed proximally The sac may then be opened widely and all the openings in the sac except the parent artery openings are sutured with silk. The tourni quet is then deflated and the sac and parent artery openings are thoroughly irrigated with normal saline solution. A vein graft of the

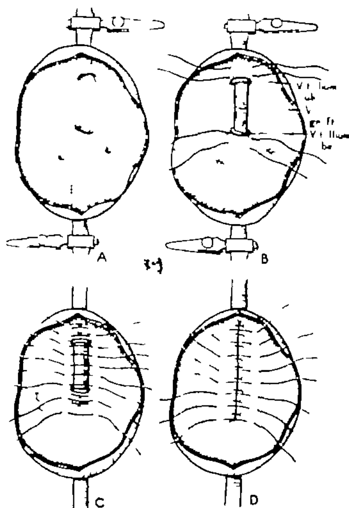


Fig. 11. Technic of intrasaccular repair of an aneurysm with vein graft inlay for the maintenance of arterial blood flow (1d)

proper length is then mounted upon vitallium tubes of the proper size and thoroughly irrigated with saline solution The aneurysmal sac is again irrigated with normal saline solution and the vitallium tube bearing the distal end of the vein is introduced into the proximal opening of the parent artery from within the aneurysm (Fig 11B) The tube is advanced far enough so that a 00 Deknatel silk suture

may be placed around the tube just proximal to the holding ridge (Fig. 11C). This suture is tied tightly using a surgeon's knot. A second silk suture with 000 Deknatel silk placed near the distal end of the tube when tied just snug approximates the artery intima to the vein intima. The vitallium tube on the other end of the vein graft is introduced into the distal opening of the parent artery and secured in an identical manner. Finally the proximal tape is released, followed immediately by release of the tape on the artery at the distal pole of the aneurysm. The opening of the anastomosis may be preceded by heparinization consisting of 20 mg. of heparin injected into the artery proximally. Anticoagulant therapy may be continued postoperatively for 3 to 5 days.

Case 4. *History.* A 42 year old Negro barber was admitted on May 29, 1945. He was known to have had a positive Wassermann reaction for 17 years before admission. Antiluetic therapy had been administered most of the time until 3 years before the present illness. The patient's Wassermann reaction became negative in 1937 and has remained so. The present illness started 2½ years before admission with a swelling of the right thigh. This occurred 2¼ years after the patient had been shot through the thigh, the bullet passing through this same area. The patient thinks that some swelling persisted following the bullet injury. During the year before admission growth of the aneurysm had been rapid.

Physical examination showed a well-developed and well nourished man looking older than his stated age. The pupils were regular, active to light and accommodation. The heart was not enlarged, with normal sounds; blood pressure in the right arm 145/100. The lungs were clear on percussion and auscultation. In the abdomen the findings were negative except for the presence of a right inguinal hernia. A pulsating mass the size of a large grapefruit was found in the right thigh in the lower Hunter's canal region. The right dorsalis pedis pulse was barely palpable.

A diagnosis of arterial aneurysm of the femoral artery was made.

Operation. Endo-aneurysmorrhaphy with vein graft inlay was performed on May 31, 1945. The operative steps have been described above. Figure 11 shows the drawings of the aneurysm and illustrates the technical stages. The vein graft was taken from the left superficial femoral vein and mounted on two 5 mm. vitallium tubes in the usual manner.

Postoperative Course Convalescence was uneventful. The wound healed by primary intention The pulse in the right foot vessels remained better than before operation but not quite as good as in the left foot (Fig. 12)



Fig 12 Arteriogram made 11 days after the procedure shown in Figure 11 (1d)

Follow-Up At 2 months postoperatively the patient was working as a barber remaining continuously on his feet. There was no swelling of the leg and the site of the aneurysm was scarcely noticeable Pulsation in the artery distal to the aneurysm remained unchanged

We now have 4 cases of peripheral aneurysms [illegible] lly treated by this technic



Fig. 13. Roentgenogram showing 2 arteriosclerotic popliteal aneurysms in an 80 year old patient (H). At left, diodrast visualization of the smaller aneurysm before wiring; note sharp angulation of the dilated and elongated parent artery proximally. At right, the large wired aneurysm 1 year postoperatively; it had reduced to 25 per cent of its original size.

There are several methods of treating arteriosclerotic peripheral aneurysms, especially in the popliteal space. Lilly (7) reported most favorably on the combined use of a chemical (alcohol) and of lumbar sympathectomy with Matas' procedure of obliterative endoaneurysmorrhaphy for popliteal arteriosclerotic aneurysms. The vitallium tube method described above preserves the collateral circulation and may be suitable in elderly individuals, but will occasionally be impossible technically because of the inelasticity and

thickening of the vein to be used for the venous graft. We have recently observed one instance where the vein graft could not be everted over a large enough vitallium tube to preserve the lumen. The electrothermic coagulation method of Blakemore (1) (Fig. 13) is a third method of handling these arteriosclerotic peripheral aneurysms

Establishment of Portacaval Shunt for Portal Hypertension

Ever since 1877 when Eck (4) a Russian physiologist successfully performed the experimental anastomosis of portal vein to vena cava surgeons have been interested in its clinical application for the relief of portal hypertension The rare reported instances (2 6,8 11–13) of attempts to establish portacaval shunts by suture and the generally discouraging results are evidence of the technical obstacles to its clinical accomplishment. The technical simplicity and efficiency of the nonsuture method of blood vessel anastomosis using vitallium tubes when employed in the anastomosis of arteries, led to its experimental and clinical trial in establishing portacaval shunts

Basic differences in the hemodynamics of the venous versus the arterial system exaggerate the importance of certain technical aspects in performing anastomoses A somewhat detailed discussion of the adaptation of the nonsuture vitallium tube method for establishing portacaval shunts therefore seems worth while

Generally speaking, technical details which are important for the success of arterial anastomosis must be executed even more meticulously to ensure the success of portacaval shunt anastomoses. Since the purpose of uniting the portal and caval systems is to reduce portal hypertension and thereby lessen the tendency to gastrointestinal hemorrhage and the formation of ascites a shunt capable of handling a large volume of blood should be established

SPLENORENAL ANASTOMOSIS

This type of portacaval shunt is capable of handling a large volume of blood in addition, it has the peculiar advantage of eliminating a sizable portion (estimated at 40 per cent) of the total circulating portal blood volume by splenectomy

Technic. The spleen is mobilized. In these cases of congestive splenomegaly extreme caution must be exercised in the control of



Fig. 14. Clamps designed by Dr. Armistead Crump for the control of blood flow during the establishment of portacaval anastomoses: the 2 large clamps may be used for occluding the vena cava; the long-handled clamps are easily applied to deep-seated vessel. (1c)

The splenic vein stump is irrigated with normal saline solution. A proper sized vitallium tube (Fig. 15D) is selected. A tube too large for the vein will present a funnel like narrowing of the latter after mounting (cuffing). The end of the vein is passed through the tube triangulated with mosquito clamps and everted (cuffed) over the end of the tube. The vein is held in place by a ligature of no. 0000

Deknatel silk placed behind a holding ridge (Fig 15A) The tube mounted splenic vein is freshly irrigated and then protected by vaseline gauze

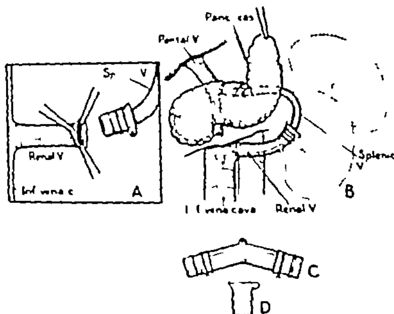


Fig. 15 Technique of splenorenal anastomosis (Ie) (A) Method of everting renal vein for introduction of vitallium tube bearing splenic vein clamp on flanged part of tube for its guidance and rubber-shod clamps on splenic and renal veins have been omitted (B) Semidiagrammatic sketch of completed anastomosis note placement of ligatures upon vitallium tube (C) Vitallium tube with vein graft mounted. (D) Improved design of vitallium tube for end-to-end or end-to-side splenorenal anastomosis There are 2 tying ridges 2 and 4 mm respectively from the end. Note tab on flange for application of holding clamp

The renal vein stump is properly trimmed and then triangulated with mosquito clamps A no 00 Deknatel silk ligature is laid loosely about the vein. The vitallium tube bearing the splenic vein is grasped with a holding clamp and the intima-covered end is directed toward the renal vein stump

Care is taken to see that neither vein is twisted They are freshly irrigated with saline following which the vein-covered end of the vitallium tube is introduced into the renal vein so that the latter comes up well proximal to the tying (holding) ridge on the tube (Fig. 15A) The previously placed silk ligature is then tied very tightly about the renal vein approximating it to the splenic vein at

a point proximal to the tying ridge upon the tube A second ligature of no. 00 Deknatel silk is placed in an identical manner Surgeons knots are essential to maintain the necessary tension in these holding ligatures Finally a ligature of 0000 Deknatel silk is tied just snug, about the renal vein approximating it to the splenic vein near the end of the tube The latter is most important, as it keeps the blood from penetrating between the two intimas Figure 15B shows completed anastomosis Release of the rubber-shod clamp on the splenic vein is arranged so as to be immediately followed by release of the rubber-shod clamp on the renal vein. The distended splenic vein should curve gently to its junction with the renal vein any tendency to acute angulation should be corrected As much peritonization of raw surfaces as is possible should be carried out and any bleeding vessels should be carefully ligated before closing the abdomen.

For several reasons resort to the use of a vein graft in performing a splenorenal anastomosis is undesirable Though tension and angulation must be avoided it is our opinion that the use of a graft is rarely necessary providing an adequate length of splenic vein is painstakingly mobilized In our experience, it has been necessary to resort to a vein graft in only 1 out of 20 cases In this case because of the unusual turgidity of the intervening tissues as a result of extreme edema the splenic vein did not adequately reach the stump of the left renal vein, though it had apparently been mobilized over a length of approximately 8 cm The gap was bridged by using a segment of superficial femoral vein In the rare case in which use of a vein graft is indicated in our belief it is best (though this point has not been proved) to employ a vein lined vitallium tube Figure 15C illustrates a vitallium tube, satisfactory in design, for this purpose

ANASTOMOSIS OF PORTAL VEIN TO VENA CAVA BY NONSUTURE METHOD

The Eck fistula type of portacaval shunt has the advantage of size An end to-end anastomosis of the portal vein to the vena cava by the nonsuture vitallium tube technic affords an estimated 30 to 40 per cent greater blood-carrying capacity than a splenorenal anastomosis

Technic To avoid the undesirable use of a vein graft, it is necessary to mobilize the portal vein from its bifurcation at the

liver to the origin of the splenic vein At the outset it is best to mobilize the descending portion of the duodenum along its lateral wall This with cutting of the peritoneum along the hepatoduodenal ligament permits adequate retraction of the duodenum medially Since the portal vein lies slightly posterior and medial to the common duct, the above maneuver facilitates medial displacement of the common duct and hence permits a lateral approach to the portal vein. Entering the abdomen through a transverse or a right rectus incision with a lateral extension has the advantage of facilitating a combined lateral and anterior approach to the portal vein. However whether the approach be combined or anterior only the common duct is mobilized sufficiently to swing it out of harm's way The portal vein is carefully mobilized by sharp and blunt dissection The placing of an umbilical tape or small Penrose tube about the vein with gentle traction facilitates its dissection The cystic vein is ligated with 0000 Deknatel silk flush with the portal vein clamped distally and cut If the pyloric vein is found at or a few millimeters proximally to the origin of the splenic vein it may be spared otherwise it is ligated with 0000 Deknatel silk and sectioned A rubber-shod clamp is placed on the portal vein at the origin of the splenic vein. A transfixion ligature of no 00 Deknatel silk is placed around the portal vein at its bifurcation close to the liver care being taken not to injure the hepatic artery or common duct. The vein is transected 4 mm distal to the ligature Finally the portal vein is irrigated thoroughly with normal saline solution using a blunt nose syringe

The vena cava is carefully mobilized by combining sharp and blunt dissection from the level of the liver down past the entrance of the left renal vein to the upper level of the right renal vein The early passage of an umbilical tape about the vena cava with gentle traction facilitates the dissection Several small vein branches will be encountered posteriorly that will necessitate ligation with 0000 Deknatel silk. A large rubber-shod clamp (Fig 14) is placed about the vena cava at the upper level of the left vein but is not tightened to occlude the vessel.

The portal vein is now passed through a vitallium tube of proper size. The end of the vein is triangulated with mosquito clamps. The tube is held firmly by a clamp The end of the portal vein is then everted (cuffed) over the end of the vitallium tube The vein is held

in place by a 000 Deknatel silk ligature tied tightly behind a tying (holding) ridge upon the tube using a surgeon s knot (Fig. 16) The vein covered vitallium tube is now swung out from behind the common duct, over the vena cava and a site for the anastomosis is selected It is most important to select a site that will not result in

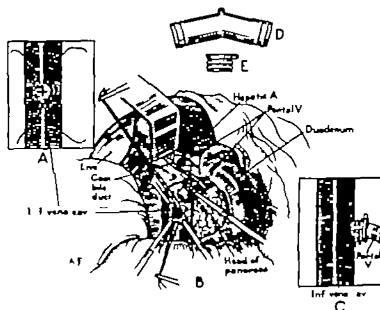


Fig 16 Technic of portacaval anastomosis (1c) (A) Placement of purse-string sutures in vena cava and centering of crucial incision for implanting vitallium tube bearing the portal vein (B) Tube bearing portal vein about to be introduced through opening in vena cava. (C) Completed anastomosis note that vena cava wall is drawn up on the vitallium tube (D) Tube of suitable design for vein graft bridging. (F) Recently designed double-ridge tube with holding tab

angulation or compression of the portal vein The portal vein is again irrigated with normal saline solution Vaseline is generously applied to the intima and the mounted vein is covered with vaseline gauze for protection

The area of anterior vena cava wall selected as the site for the anastomosis is cleared of adventitia. Now thoroughly tested no 00 Deknatel silk threaded on a small Ferguson needle, is introduced as a purse-string suture in the vena cava wall (full thickness) at the chosen site The silk should be well coated with vaseline before its introduction. The purse-string suture is introduced to form a circle

the diameter of which is 4 mm larger than the diameter of the vitallium tube selected for the anastomosis. A second circular purse-string suture starting at the opposite side (Fig. 16A) is placed 2 mm outside of the first one. A second rubber-shod clamp is put in position about the vena cava as close to the liver as possible. The distal rubber-shod clamp is now quickly tightened so as to occlude completely the vena cava at the upper level of the left renal vein followed by tightening of the proximal rubber-shod clamp. The time at which the occlusion is made is noted and recorded. A crucial incision through the vena cava wall, its length not exceeding the diameter of the vitallium tube, is centered exactly within the inner purse-string area. The apex of each quadrant of vena cava wall thus formed is grasped with mosquito clamps and the vena cava is irrigated using several syringeful of normal saline solution.

The first turns of a surgeon's knot are placed in each purse-string suture but not tightened. The vitallium tube bearing the portal vein is grasped with a clamp and advanced through the opening into the vena cava again that steady countertraction upon the mosquito clamps (Fig. 16B). The vitallium tube must not be rotated, as this produces twisting of the portal vein. The vena cava is pulled well up on the vitallium tube so that the inner purse-string suture, as it is tightened, will fall proximal to the tying (holding) ridge on the tube. The purse-string suture is finally drawn very tight and the surgeon's knot completed. The holding clamp on the vitallium tube may now be removed and the second purse-string suture tied just snug about the vitallium tube. The latter will, if correctly placed, tighten about the tube just proximal to the distal ridge. The mosquito clamps may now be removed. Figure 16C shows the completed anastomosis.

To establish blood flow through the anastomosis first release the proximal rubber-shod clamp on the vena cava. Next release the rubber-shod clamp on the portal vein and follow immediately by release of the distal rubber-shod clamp on the vena cava. Duration of occlusion of the vena cava is noted and recorded. Finally, the portal vein is inspected for angulation or constriction. Any change of position is noted during the return of the duodenum to its normal position. Omentum may be placed over any unperitonized surfaces. Hemostasis should be checked and the abdomen closed carefully in layers.

Should the use of a vein graft to complete the anastomosis be unavoidable, the external iliac vein more nearly approximates the

diameter of the portal vein, and only a short segment (6 to 7 cm.) is required. Figure 10D illustrates a satisfactory design of a vitallium tube to be lined by a vein graft.

CASE REPORTS ILLUSTRATING THE TWO TYPES OF PORTACAVAL SHUNTS

Case 5. This case illustrates the use of a single vitallium tube to establish a splenorenal anastomosis.

History. A. P., a 5 year old girl, was first admitted to Presbyterian Hospital in October 1942 with the complaint of abdominal enlargement of 3 months' duration. Family and past history was noncontributory. Present illness consisted in onset with progressive enlargement of the abdomen and anorexia. The mother had noticed an increasing tendency to bruise following minor traumas. On physical examination, the child appeared chronically ill. The pertinent findings were confined to the abdomen. The latter was protuberant, with visibly distended venous channels. There was no free peritoneal fluid. The liver was enlarged 8 cm. below the costal margin and was firm with a sharp border. The spleen extended 10 cm. below the costal margin and was very firm. Studies revealed a moderate derangement of liver function. The diagnosis was portal cirrhosis, congestive splenomegaly. The child was placed on a high protein high vitamin diet and discharged on December 1, 1942.

She was readmitted to Presbyterian Hospital on May 25, 1943. The general condition was unimproved. On examination, the child was decidedly anemic. The liver and spleen were as enlarged as before. Three transfusions were given during the next 2 weeks. A stool examination was positive for blood. Though an esophagram failed to show varices, on the fifteenth day after admission the child began to vomit large quantities of blood. For several days blood replacement was carried out by continuous transfusion. During the ensuing month the child's condition remained desperate. Her hemoglobin could not be maintained above the low forties. The ascites that had supervened became irreversible.

Operation. On July 20, 1943, the child's abdomen was explored in the hope that the blood could be shunted from the portal to the caval system by a splenorenal anastomosis, employing the nonsuture method.

The liver was found to be decidedly cirrhotic the spleen 8 to 10 times the normal size There was considerable collateral circulation between the splenic gastric and omental vessels Ascites was present The right and left kidneys appeared normal

A long left rectus incision was made The spleen was mobilized and the splenic artery ligated The splenic vein was closed by a serrefine clamp sectioned near the spleen and the spleen was removed The splenic vein was then dissected proximally for a distance of 6 cm and irrigated with isotonic sodium chloride solution. The tail of the pancreas and the left kidney were mobilized The renal artery and ureter were ligated and cut The renal vein was mobilized throughout its length a serrefine clamp was applied proximally and the vein was sectioned near the kidney

The end of the splenic vein was passed through a special vitallium tube everted (cuffed) over the tube and held in place by a 0000 Deknatel silk ligature tied tightly behind a holding ridge on the tube some 5 mm. from the end The stumps of the renal and splenic veins were irrigated with isotonic sodium chloride solution. The vitallium tube bearing the cuffed end of the splenic vein was then introduced into the stump of the renal vein The latter was drawn well up on the tube and secured by a no 00 Deknatel silk ligature passed around the 2 veins over the tube and tied tightly behind the holding ridge This provided a broad contact of splenic vein intima to renal vein intima. A second ligature of 000 Deknatel silk was tied just snug near the end of the vitallium tube to prevent the penetration of blood between the intima Heparinization consisted of 15 mg. of heparin, intravenously The serrefine clamp on the splenic vein was removed quickly followed by removal of the serrefine clamp on the renal vein. This opened the anastomosis and blood rushed through from the portal system via the splenic vein into the caval system via the renal vein The abdomen was closed with near and far wire sutures the skin with interrupted silk sutures The patient left the table in fair condition having received a transfusion of plasma and blood during the operation

Postoperative Course Administration of heparin by intravenous drip was continued for 2 days On the second day the patient became distended, dyspneic and stuporous The temperature rose to 104 F oliguria developed moist rales appeared throughout the lungs the nonprotein nitrogen rose to 85 mg. per 100 cc The exact cause of the

unfavorable course was not established but it was felt that hepatorenal failure was a contributing factor A duodenal tube was passed and large amounts of fluid recovered. Massive parenteral doses of vitamin B complex were administered. The results were sudden and dramatic Kidney function improved Nonprotein nitrogen dropped to 43 mg. per 100 cc on the fifth postoperative day, and from then on convalescence was uneventful



Fig 17A Patient with splenorenal anastomosis established by the use of one vitallium tube (II) Infra-red photograph of superficial collateral veins 20 days after portacaval shunt was established

Pathologic Findings Microscopy revealed that various sized liver cells were accumulated in large and small islands between wide bands of connective tissue Microscopic sections of the spleen showed *the usual picture of congestive splenomegaly* Numerous cysts, 0.5 to 2 0 mm. in diameter and lined with flattened epithelium were scattered throughout the cortex and medulla of the left kidney In addition there were small wedge-shaped areas of scarring and cellular infiltration in these the glomeruli were sclerotic and tubules dilated and filled with hyaline casts Lymphocytes predominated in the cellular exudate.

The diagnosis of congenital cystic kidney with a superimposed infection was discouraging.

Follow Up. In spite of the initially poor prognosis, at 7 months postoperatively the patient had gained 4 lbs. (1.8 Kg.), her appetite was good and she played actively. The ascites had not recurred. The superficial collateral veins over the abdomen had receded. The hemoglobin had increased (12.5 Gm.). A stool guaiac test for blood gave negative result. A concentrated urine specimen showed many



Fig. 17B. Appearance 15 months later of same patient as in Figure 17A (1b).

hyaline casts, a few red and white blood cells, a specific gravity of 1.009 and a faint trace of albumin. Nonprotein nitrogen was 48.9 mg. per 100 cc., urea ratio 50.0. Phenolsulfonphthalein excretion was 50 per cent. The blood pressure determined repeatedly ranged from 110/70 to 120/80.

Re-evaluation 12 months postoperatively, on July 17, 1944, disclosed that the appetite was good, the patient was gaining weight and there were no bleeding episodes although the mother stated that the child "bruises easily." Blood pressure was 124/76. Superficial abdominal veins were not prominent and there was no edema or ascites. The liver edge was 6 cm. below the costal margin. The

laboratory findings were hemoglobin 11 3 Gm red blood cells 3,500 000 specific gravity of urine 1 016 faint trace of albumin in urine and a few white blood cells on microscopic examination nonprotein nitrogen 46 4 mg. per 100 cc urea nitrogen 36 7 mg. per 100 cc urea ratio 79 1 total proteins 7 6 per cent albumin, 4 08 per cent globulin 3.53 per cent stool guaiac test for blood gave negative results

The liver function tests before the operation and 6 and 12 months postoperatively may be summarized as follows Protein partition remained unchanged (albumin–globulin ratio was never reversed) An elevated prothrombin time before operation dropped to normal after operation A preoperative cephalin flocculation test result of 3 plus and an increased bromsulfalein excretion surprisingly fell to normal postoperatively The results of the galactose tolerance and hippuric acid conjugation tests indicated increased liver impairment.

The patient continued to do well until October 8 1944 when she felt weak dizzy and passed 3 tarry stools Her mother reported a recent nosebleed She was admitted to Babies Hospital and given multiple transfusions over a period of 8 days The initial hemoglobin of 50 per cent rose to 82 per cent The liver was enlarged as before no ascites was present. Even after the blood volume was completely restored no increase was noted in distention of the superficial abdominal veins (Fig 17A–B) The nonprotein nitrogen level upon hospital admission was 90 mg per hundred cubic centimeters 2 days later it had dropped to 47.9 mg The figure on admission was higher than had been recorded during the days of hepatorenal failure immediately after operation (85 mg./100 cc) The diastolic blood pressure was consistently higher on this admission and the systolic somewhat higher During the 1 1/4 years since operation height had increased from 40 to 44 3/4 in (102 to 112 cm) and weight had increased from 33 to 48 lbs (15 to 22 Kg)

She was discharged on October 21 1944 The stool guaiac test at that time was negative

Summary A 5 year old child diagnosed as having portal cirrhosis after 8 months developed massive hemorrhages from esophageal varices and ascites A portacaval shunt was established following removal of the spleen and left kidney Examination of the kidney revealed the additional diagnosis of congenital polycystic disease The general health of the child improved decidedly after operation, and this improvement was maintained over a period of 15 months.



Fig. 18A Patient in whom vein graft bridging established a splenorenal anastomosis (1c). Infra-red photograph of superficial collateral veins, marked distention of abdomen with ascites and bulging umbilical hernia.



Fig. 18B Same patient as in Figure 18A 5 months post-operatively (1c).

There was improvement in some of the liver function tests and no return of the ascites. Frequent examinations of the kidney however showed gradually increased impairment. At 14 months postoperatively the child had a nosebleed and a few days later passed 3 tarry stools. The blood pressure (systolic and diastolic) averaged higher than previous levels and the nonprotein nitrogen was 90 mg. per 100 cc. She responded to transfusions and is now back at school. At 2 years following operation she is active and remains symptom free.



Fig. 19. Roentgenogram of abdomen. On the left are 2 vitallium tubes, one on either end of vein graft between splenic and left renal veins. On the right, a vitallium tube that had been used at a previous operation to bridge a defect in the common bile duct.

Case 6. This case illustrates vein graft bridging in a splenorenal vein anastomosis using 2 vitallium tubes.

History. E. M., a 46 year old white man, entered Presbyterian Hospital on November 8, 1944, for the tenth time complaining of

epigastric pain. He was first seen in 1937 because of a 2 year history of epigastric pain temporarily relieved by diet. A gastrointestinal roentgen series showed a lesion of the second portion of the duodenum, interpreted as being malignant.

At operation an infiltrating tumor mass was felt at the junction of the first and second portions of the duodenum involving the head of the pancreas. A posterior gastroenterostomy was performed. Because jaundice developed postoperatively, a cholecystojejunostomy and jejunojejunostomy were carried out.

During the next 3 years 2 operations were performed because of intermittent jaundice. In 1941, an exploratory laparotomy was carried out, and in 1942 a stone was removed from the common bile duct and the latter anastomosed to the stomach over a vitallium tube.

From 1942 to 1944, the patient slowly but progressively developed signs of biliary cirrhosis with portal hypertension.

Physical examination revealed a cachectic appearing white male with massive ascites and slightly jaundiced. The abdomen showed in addition to the ascites, numerous markedly distended veins. There were 2 vertical and 1 transverse operative scars on the right, with a ventral hernia 10 cm in diameter near the medial end of the transverse scar (Fig. 18A). The liver edge was palpable 8 finger breadths below the right costal margin, the spleen 2 fingerbreadths below the left costal margin.

The interesting laboratory findings were: 0.4 Gm. hippuric acid excreted in 1 hour (normal 1 or more grams); serum bilirubin, 2 mg. per 100 cc.; result of cephalin flocculation test, 1 plus; albumin-globulin ratio 3.2/2.5 per cent.

Operation. This was performed on November 30, 22 days after admission to hospital. The spleen and left kidney were removed. Because extensive tissue edema made it impossible to bring the splenic vein into apposition with the renal vein, a 10 cm. segment of the right femoral vein on two 5 mm. vitallium tubes was used to bridge the gap between the ends of the splenic and renal veins (Fig. 19). The liver was somewhat enlarged and firmer than normal, but did not appear definitely cirrhotic. The spleen weighed 700 Gm., after removal.

Postoperative Course. Ascites reaccumulated to such an extent that two paracenteses were necessary. At the time of discharge, the

serum bilirubin was 1 mg per 100 cc., the albumin–globulin ratio, 3.5/3.2 per cent.

Follow-Up Repeated paracenteses were necessary during the first 6 weeks, but after February, 1945 the ascites completely disappeared. At 5 months postoperatively, the results of the cephalin flocculation test were normal, the albumin–globulin ratio was 3.8/3 1 per cent the bromsulfalein test showed 25 per cent retention after 30 minutes (approximately the same as preoperatively) hippuric acid excretion was 0.96 Gm. in 1 hour (0 4 Gm preoperatively) The general condition was excellent (Fig. 18A–B)

Case 7 This is an illustration of the use of a vein lined tube to effect an anastomosis between the portal vein and the vena cava.

History S. S a 25 year old white man, had been followed at Presbyterian Hospital since 1938 for cirrhosis of the liver At that time, splenectomy had been performed because the spleen was large and there had been repeated hematemeses the liver in the gross, showed a moderate degree of cirrhosis. During the next 6 years, the patient remained fairly well episodes of hematemesis recurring only during 1944 Studies then showed a moderate impairment of hepatic function with jaundice (serum bilirubin 4.5 mg./100 cc.) and ascites. His anemia failed to respond well to repeated transfusions and appropriate iron and liver therapy and intermittent hemorrhages from esophageal varices continued An operation was therefore performed on March 2 1945

Operation. The cirrhotic changes in the liver were more marked than at the operation in 1938 and the branches of the portal vein were under tension. Because the end of the portal vein could not be made to reach the inferior vena cava easily a segment of the right femoral vein was used to line a straight vitallium tube, and this served to connect the portal vein with the vena cava in an end-to-side anastomosis. Roentgenography of the abdomen showed that the tube was in place

Postoperative Course The course was stormy chiefly as a result of an evisceration on the tenth postoperative day following the cutting of the steel wire sutures Recovery from secondary closure was successful but on the fiftieth postoperative day an appendectomy had to be performed because of signs and symptoms of acute appendicitis. The patient was discharged in fair condition on the sixty fifth postoperative day

Follow-Up During the 2 months following discharge patient gained 16 lbs. jaundice had cleared there was no evidence of ascites. The result of the cephalin flocculation test was the same as preoperatively—3 plus The total proteins were 8.8 per cent, albumin–globulin ratio 2.5/5.3 per cent, nonprotein nitrogen, 19 mg. per 100 cc At 6 months postoperatively the patient was in excellent condition working daily driving a delivery truck. No jaundice or ascites were present.*

SELECTION OF CASES FOR PORTACAVAL ANASTOMOSIS

The portacaval shunt operation is indicated in cases of splenomegaly exhibiting the now familiar Banti s syndrome, cases in which the block in the portal system is extrahepatic. There is no medical treatment for such cases and follow up experience in the Spleen Clinic of Presbyterian Hospital reveals that splenectomy fails to protect against lethal hematemesis

It is our opinion that a portacaval shunt operation should be attempted even though the patient had been subjected to splenectomy at a previous operation It is true that in our experience with this group a portacaval shunt of the Eck fistula type (portal vein to vena cava) has not been feasible because of cavernomatous transformation or atresia of the portal vein. In 2 patients with Banti s syndrome, who had previously had splenectomies we effected a portacaval shunt by anastomosing the stump of the splenic vein to the side of the vena cava in one. In the other case, the splenic vein was anastomosed to one branch of a bifurcating renal vein following nephrectomy The remaining branch of the renal vein was anastomosed end to-end with the proximal stump of the inferior mesenteric vein. The inferior mesenteric vein joined the superior mesenteric vein in this case.

Patients of the Banti group in our experience have consistently shown a high portal pressure reading. It is true that splenorenal anastomoses have usually resulted in a substantial reduction in the portal pressure. It is regrettable, however, that in none of the Banti group so far operated upon has it been feasible to make use of the larger blood-carrying potentialities of the portal vein to vena

* For an up-to-date analysis of cases operated upon, see Tables IV and V

cava anastomosis on account of the high incidence of cavernomatous transformation or atresia of the portal vein. Without operation, patients with Banti's syndrome are doomed. The splenorenal shunt does offer a chance of diminishing the severity of the bleeding attacks, if not complete relief

Patients with portal hypertension due primarily to portal cirrhosis of the liver make up another large group that come up for consideration. Our present policy *in general is to recommend the portacaval* shunt procedure only in those cases in which a modern medical regime has failed In other words, cases in which there is substantial evidence that portal hypertension not liver insufficiency due to inadequate prothrombin formation is the primary cause of hemorrhage

It is now known that prothrombin disappears rapidly from the blood stream.

One of us (A H. B) repeatedly noted ecchymosis in the surgical wounds of cases of aneurysms of the aorta following wiring and electrothermic coagulation. In these cases, at the time of heating segments of insulated wire within the aneurysm the inferior vena cava just proximal to the entrance of the hepatic veins was obstructed for 5 minute periods. This was achieved by introducing a ureteral catheter bearing a condom balloon into the great saphenous vein and up the common femoral vein through the abdominal vena cava just through the diaphragm. Normal saline solution was then injected into the balloon via the catheter to effect an obstruction of the vena cava. The purpose of this procedure was to diminish cardiac output and rate of blood flow through the aneurysm to encourage clotting during the period of heating the wire within the aneurysm The rate of blood flow through aneurysms could be reduced by as much as 50 per cent when this method was used the only untoward effect noted, and this invariably was ecchymosis of the skin incisions. Our suspicions that prothrombin deficiency caused the ecchymoses was confirmed by one of us (J W L., Jr) by carrying out the identical procedure on dogs, namely obstructing the vena cava immediately above the diaphragm for 4 or 5 periods of 5 minutes each during a total period of 2 hours. Apparently the obstruction to the outflow of blood from the liver through the hepatic veins was sufficient to impair the prothrombin formation in the liver because for some hours after the procedure the prothrombin times remained elevated to hemorrhagic levels.

The likelihood that interference with blood flow through the hepatic veins may cause derangement in prothrombin formation by the liver is further suggested by the case of a young woman now

under our care—a case in which a liver biopsy led to a diagnosis of thrombosis of the hepatic veins some 10 months ago.

It seems likely that in many cases of cirrhosis of the liver the initial hemorrhage may have been the result of a deficiency in prothrombin. These are often cases with large fatty livers and little or no evidence of portal hypertension. As an illustration we cite the case of a patient we are now observing, in whom the diagnosis of cirrhosis was made at the time the uterus was being removed for unexplained metrorrhagia. The enlarged liver was not treated and some 6 months later the patient began to have hematemesis. These episodes recurred at monthly intervals for 5 months before the patient was placed on a liver therapy regime as now practiced. Liver function studies at the time the medical regime was started revealed a badly functioning liver The patient came under our care some 3 months later, while no bleeding episode had occurred for 3 months the prothrombin time was still considerably elevated and did not return to normal until 6 months after the liver regime had been instituted. It is now 9 months since the last hematemesis. The liver is considerably reduced in size and esophograms finally show small varices. In the interim, the patient gained weight and strength. The albumin-globulin ratio is normal and the bromosulfalein excretion is improved. Hemorrhages in this case started in the uterus on a prothrombin deficiency basis. Not only was a portacaval shunt not indicated during this interval but the patient would have been a decidedly poor operative risk. We grant that with the appearance of esophageal varices the likelihood of a return bout of hemorrhage is increased but the patient is now a far better operative risk. Prothrombin time is now normal and the indications for a portacaval shunt would be squarely based on the relief of portal hypertension as a cause of the recurrence of hematemesis Other cases similar to the above made us feel strongly that the portacaval shunt should not be undertaken as a heroic measure to save life from hemorrhage until prothrombin deficiency can be ruled out as a primary cause.

The portacaval shunt operation is contraindicated in those cases of cirrhosis which are decompensated to the point where prothrombin deficiency exists in the blood within the range of spontaneous hemorrhage. If such patients cannot be improved by a vigorous medical regime (as many can) they are doomed to die The above

statement does not mean that one cannot operate successfully on patients with badly damaged cirrhotic livers, i.e., badly damaged as shown by the usual liver function tests. For example, we have had several patients survive the operation who had varying degrees of jaundice; some have shown bromsulfalein retention of as much as 60 per cent half an hour after injection, and there have been several who had preoperative reversals of the albumin–globulin ratio. Other things being equal, such cases are obviously not as good operative risks; operation was the last resort, other measures failing.

To summarize, the portacaval shunt operation should be employed for the relief of recurring attacks of gastrointestinal bleeding only in those cases of cirrhosis of the liver in which there is good evidence that portal hypertension is the responsible factor. Operation is contraindicated in cases having a prothrombin deficiency which fails to respond to a dietary liver regime.

INDICATIONS FOR PORTACAVAL SHUNT OPERATION FOR RELIEF OF ASCITES

Under what condition should the presence of ascites be considered an indication for establishing a portacaval stunt in cases of cirrhosis of the liver? This question may best be answered by citing the following cases.

(*1*) In late January, 1946, a 49 year old man with ascites due to alcoholic cirrhosis was admitted to Presbyterian Hospital for operative consideration. This patient had been under the care of an excellent internist and had been thoroughly studied at the Lakeside Hospital of Cleveland. For 4 months he had followed an excellent medical regime for cirrhosis of the liver without any apparent beneficial effect upon the ascites. However, upon his admission to Presbyterian Hospital, he volunteered the information that he believed his ascites was less though the time for paracentesis was a week overdue. The patient's observation proved correct, during the ensuing several weeks the ascites largely disappeared. A 4 month liver regime had effected a turning point in his ascites just at the time a portacaval shunt operation was being seriously considered. An ascites of 5 months' duration, because of the large amount of fluid formed, had constituted a great handicap to this man; he had been unable to work, and was most anxious to have a portacaval shunt operation

While the patient's liver was hard and nodular, and the bromsulfalein excretion was below normal, we advised against operation at this time for the following reason (a) There had been no episodes of bleeding. (b) Total blood proteins were normal, with a normal albumin–globulin ratio The improvement of this patient's protein values in comparison with the results of a previous study at the Lakeside Hospital, plus the disappearance of his ascites led us to conclude that portal hypertension was not an important factor in this case at this time. It must be kept in mind, however, that in spite of the excellent response to a dietary regime in the above case, peri portal fibrosis may continue, and in time a portal hypertension of such magnitude may develop as to cause a recurrence of the ascites. The following case well illustrates this point.

(2) A 55 year old woman, having a long alcoholic history, a year previously began to have anorexia and weakness followed, in a few weeks by the appearance of ascites. She was hospitalized and a thorough liver chemistry study was made. The total blood proteins were low and the albumin–globulin ratio was reversed. The brom sulfalein and other liver function tests revealed serious impairment of liver function. The liver was hard and greatly enlarged. Roentgenograms of the esophagus revealed no varices. The patient was placed upon a Patek liver regime, and after a few weeks her appetite and strength began to improve. The ascites gradually disappeared as the blood proteins rose Through the summer months the patient was in excellent condition and free of ascites. Though her appetite nutrition, and strength remained excellent, the patient began to develop ascites in October However the blood proteins level at this time was excellent, and the liver function tests gave better results than before. The liver had shrunk considerably over a 6 month period. From October through December the ascites became worse, requiring increasingly frequent paracenteses. Evi dence of increased portal pressure was observed for the first time upon roentgenographic demonstration of esophageal varices. In the early months of 1946 while the patient's appetite remained good she could not eat adequately at any one feeding on account of the ascites. Though it was demonstrated that this patient's liver could make albumin in normal amounts the ascitic fluid contained a fair percentage of protein the removal of large quantities at 5 day intervals finally began to lower her total blood proteins and spell

TABLE I Protein Values in Eight Cases of Portal Cirrhosis of the Liver

Case no.	Age	Sex	Condition	Operation	Proteins, mg./100 cc. Preoperative Total proteins	Preoperative Albumin	Preoperative Globulin	Postoperative* Total proteins	Postoperative* Albumin	Postoperative* Globulin
1	27	M	Esophageal varices	Splenorenal shunt	6 6	2 9	3.7	7.1	3 6	3.9
2	47	F	Esophageal varices	Eck fistula	7.8	4 3	3.5	5 6	3.4	2 2
					8.1	3.9	4 2	6.6	4.1	2.5
					8.0	4.1	3.9	6.1	3.8	2 4
3	5	F	Ascites esophageal varices	Splenorenal shunt	8.2	4 5	3.7	7 4	3.5	3 9
								7.2	3.7	3.5
								7.2	4.1	3.1
								7.5	3.8	3.5
4	28	M	Esophageal varices	Eck fistula vein graft	8 6	3.3	5.2	6.9	2.6	4.3
								7.1	2.4	4.7
								7.9	2.2	5.7
								8.8	(1.5)	6 8
								6.2		4.7
								7 4	2.2	5.1
5	42	M	Ascites esophageal varices	Splenorenal shunt	7.5	3.5	4.0	6 2	2.5	3.7
								6.8	2 6	4.2
								6.5	2.6	3.9
6	55	M	Esophageal varices	Splenorenal shunt	5.7	3.2	2.5	6 4	3.7	2.7
					7.1	3.8	3.3	7.2	4.1	3.1
					6 4	3.5	2.9	5 8	3.1	2.7
								6.5	3.6	2.8
7	49	M	Ascites	Eck fistula	5 3	2.3	3.0	5.9	3.6	2.3
								5.4	2.6	2.8
								5.7	3.1	2.6
8	58	M	Ascites	Eck fistula	5 2	2 9	2.3	4 5	2.5	2.0
								4.9	2 3	2 4
								4 7	2.9	2.0
								5 0	1.9	3.1
								5 0	2 0	3 0
								5 0	2.2	2.8

her doom. The recurrence of ascites in this case paralleled the development of evidence of severe portal hypertension, and this patient's one and only chance of survival therefore rested upon the successful accomplishment of a portacaval shunt.

The lesson to be learned from this case is that the patient was doomed not because of liver insufficiency but because of a wasting ascites due to portal hypertension. It is a fact that wasting ascites is the predisposing factor leading to death in many cases of cirrhosis.

The present medical and dietary regime will often do wonders in reviving a damaged liver in varying states of decompensation. A sustained improvement in liver function may result. On the other hand there is no reason to expect that such a regime will necessarily affect fibrotic contraction of the liver or periportal fibrosis which are pathologic processes of a predetermined course based on damage already done.

The indications for a portacaval shunt in cases of portal cirrhosis may be summarized and clarified by classifying cases of cirrhosis in 3 groups. (*1*) Cases in which ascites or a tendency to hemorrhage is based on the inability of the damaged liver to form albumin or prothrombin in adequate amounts. Portacaval anastomosis is not indicated in this group. (*2*) Cases of cirrhosis in which liver function is adequate to furnish the required amount of protein and prothrombin, but in which as a result of fibrotic contraction and periportal fibrosis, a severe degree of portal hypertension has supervened. Wasting ascites and severe hemorrhage can only be controlled in this group by the portacaval shunt. (*3*) Cases of cirrhosis having varying degrees of depressed liver function plus evidence of considerably increased portal pressure. Such cases are candidates for the portacaval shunt operation. The question is: when? Our present policy is to study each case with exceeding care, whenever it is possible, over a long enough time to become thoroughly familiar with the behavior of the liver before the case is brought to operation. This is always possible with patients who are not subject to recurring hemorrhages. The intention is to improve liver function to its maximum, employing a comprehensive, energetically applied liver regime for as long a period as necessary.

Sufficient time has elapsed (1 or more years) since operation for follow up data to have some significance in 8 cases of cirrhosis. The protein values in these 8 cases are given in Table I.

Ascites disappeared following operation in the 4 cases in which it had been present (cases 3, 5, 7, 8). In cases 3, 4, and 6 the operation was performed as a life-saving measure to control persistent hemorrhage. Case 3 died of uremia due to polycystic disease and chronic nephritis some 2½ years following operation. Systemic

TABLE II

Bromsulfalein Liver Function Test in Seven Cases of Portal Cirrhosis of the Liver

Case no.*	Bromsulfalein retained 30 minutes after injection			
	Preoperative		Postoperative	
	Dye, per cent	Remarks	Dye, per cent†	Remarks
1	70		38	
2	45		10 30 *20*	
3	10		5 10 *8*	
4	42		40	
5	60	Serum bilirubin, 1.5 mg./100 cc.	65	Serum bilirubin, 2.5 mg./100 cc.
6	20	Serum bilirubin, 3.5 mg./100 cc.	22 25 35 *27*	Serum bilirubin, 1 mg./100 cc.
8	35		35 20 *27*	Serum bilirubin, 3 mg./100 cc.
		Serum bilirubin, 4 mg./100 cc.	61 55 *39*	No jaundice

* Same series of cases as in Table I.
† Italicized figures are averages.

arterial hypertension developed and toward the end there was one episode of hemorrhage causing tarry stools but no hematemesis such as had occurred before operation. In case 4 there has been one slight episode of hemorrhage in the course of 1½ years since operation. In case 6 there have been several episodes of hemorrhage since operation. In this case, a splenorenal shunt was accomplished with the aid of a segment of superficial femoral vein which in our

following operation, while in the remaining 5 (cases 2, 3, 4, 5, and 8) there was a slight fall in both total proteins and albumin. Cases 3, 5 and 8 had ascites before operation. The disappearance of the ascites following the establishment of portacaval shunts in these cases, in spite of the lowered proteins, emphasizes the role of portal hypertension as a causative factor.

Table II records the results of the bromsulfalein liver function tests in 7 cases of cirrhosis before and after the establishment of portacaval shunts. The accuracy of the test must be discounted in the 3 cases (5, 6, and 8) having varying degrees of jaundice.

The results of the hippuric acid liver function test, the cephalin flocculation test, and the prothrombin time in the cases tested before and after operation are listed in Table III.

In conclusion, it may be stated that portacaval anastomoses afford the sole chance of ultimate survival for patients with extrahepatic portal block in which there is hypertension in the portal or coronary veins.

The portacaval shunt operation has an equally important role in the treatment of portal hypertension resulting from cirrhosis of the liver. But its application in cirrhotic patients must be determined on the basis of whether portal hypertension is the primary cause of the ascites or hemorrhage.

TABLE IV Abstract of Eighteen Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Extrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Liver chemistry	Blood dyscrasia	Operation	Pathology	Follow-up
1	14, F	Hematemesis	Splenomegaly Esophageal varices	Normal	Pancytopenia	6/22/44, splenorenal shunt, nonsuture	Congestive splenomegaly; atresia of splenic vein	7 months postop. recurrence of hemorrhage; died of hematemesis 3 yrs. 9 mos. postop.
2	2, F	Hematemesis	Splenomegaly Esophageal varices	Normal	Sec. anemia Leukopenia	9/16/46, splenorenal shunt, suture	Congestive splenomegaly; cavernomatous transformation of portal vein	Return of bleeding 4 mos. postop.; died of hemorrhage 1 yr 8 mos. postop.; necropsy showed shunt to be closed
3	30, M	Hematemesis	Splenomegaly Esophageal varices	Ceph. floc. ++	Pancytopenia	2/8/46, splenorenal shunt nonsuture	Congestive splenomegaly; liver biopsy essentially normal	Well, no further hemorrhages
4	9, M	Hematemesis	Splenomegaly Portal hypertension	Ceph. floc. ++	Pancytopenia	4/11/46, splenorenal shunt, nonsuture	Congestive splenomegaly; liver biopsy no cirrhosis	Well, no hemorrhages
5	12, F	Hematemesis	Splenomegaly Esophageal varices	Ceph. floc. ++	Sec. anemia Leukopenia	5/16/46, splenorenal shunt, nonsuture	Congestive splenomegaly	1 hematemesis 2/8/48 (1.5 yrs. postop.)
6	36, M	Hematemesis	Splenomegaly Esophageal varices	Ceph. floc. + Bromsulf. retention 80% after 5 min., 18% after 0.5 hr	Sec. anemia Leukopenia	11/14/46, splenorenal shunt, nonsuture	Cavernomatous transformation of portal vein; normal liver	Death 20th postop. day from mesenteric thrombosis starting from old thrombus in portal vein
7	6, F	Hematemesis	Splenomegaly Esophageal varices	Normal	Pancytopenia	4/20/46, splenorenal shunt, nonsuture	Congestive splenomegaly normal liver	Well, no hemorrhages
8	23, M	Hematemesis (splenectomy 1939)	Esophageal varices	Normal	Sec. anemia	2/1/47 inf. mesenteric vein to left renal vein, nonsuture	Normal liver	14 mos. postop. patient passed tarry stool once
9	9 M	Hematemesis	Splenomegaly Hepatomegaly	Ceph. floc. +++ Bromsulf. normal	Pancytopenia	1/10/47 splenorenal shunt, nonsuture	Normal liver by biopsy; congestive splenomegaly	Well, no hemorrhages
10	6, M	Hematemesis	Splenomegaly Esophageal varices	Normal	Pancytopenia	7/29/47 splenorenal shunt, suture	Congestive splenomegaly; normal liver	Well, no hemorrhages

continued

Table IV (*concluded*) Abstract of Eighteen Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Extrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Liver chemistry	Blood dyscrasia	Operation	Pathology	Follow-up
11	16, M	Hematemesis	Splenomegaly	Normal	Pancytopenia	1/4/47, splenorenal shunt, suture	Congestive splenomegaly; normal liver	Well, no hemorrhages
12	31, F	Hematemesis	Splenomegaly Esophageal varices	Ceph. floc. ++	Pancytopenia	10/28/47 splenorenal shunt, suture	Congestive splenomegaly normal liver	Well, no hemorrhages
13	23, F	Hematemesis	Splenomegaly Esophageal varices	Ceph. floc. +++ Thymol turbidity ++	Pancytopenia	10/23/47, splenocaval shunt, suture	Congestive splenomegaly secondary to congenital arteriovenous shunts between splenic artery and vein	Death on 2nd postop. day from encephalomalacia secondary to thrombotic occlusion of mid and anterior cerebral arteries
14	12, F	Hematemesis (splenectomy 1946)	Splenomegaly Esophageal varices	Ceph. floc. +++	Pancytopenia	9/12/47 sup. mesenteric vein to vena cava, side-to-side	Normal liver; congenital absence of splenic vein	Hematemesis recurred 4 mos. postop.
15	48, M	Hematemesis (9 attacks in 11 yrs.)	Hepatosplenomegaly Esophageal varices	Ceph. floc. neg. Thymol turbidity neg.; bromsulf. retention 0.5 hr 15%	Pancytopenia	6/2/48, splenorenal shunt, suture	Liver biopsy normal	Esophogram showed marked reduction in size of varices; no further hemorrhages
16	20, F	Hematemesis 1935 and 1940. Splenectomy Recurrences 1942 and 1943. Ligation and injection l. gastric artery Recurrence melena 1947	Esophageal varices	3/4/48, bromsulf. retention 0.5 hr 5%; serum alb. 4.7%, glob. 2.3%	Sec. anemia	3/11/48, sup. mesenteric to vena cava, end-to-side, suture	Normal liver (gross and biopsy)	Recurrent hematemesis 5/22/48
17	18, F	Splenectomy for hematemesis in 1940. Hemorrhages recurred	Esophageal varices	Normal	Sec. anemia	9/17/48, stump of splenic vein to renal vein, suture	Normal liver	Well, no hemorrhages since discharge
18	9, M	Splenectomy Ligation esophageal veins 1944. Recurring hematemesis	Bronchiectasis Esophageal varices	Normal	Sec. anemia	11/1/48, stump of splenic vein to vena cava, suture	Liver biopsy normal	Over 2.5 yr follow-up there have been 2 major episodes of hemorrhage (hematemesis and melena) compared to 3 major attacks during year prior to operation

TABLE V

Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
1	6, F	Treated for liver cirrhosis 1 yr; hematemesis	Splenomegaly Portal cirrhosis Esophageal varices Ascites, polycystic disease of kidneys	Serum alb. 4.3%, glob. 3.6% Bromsulf. retention 0.5 hr 10% Cephalin floc. 4+	Secondary anemia Leukopenia	7/26/43 Splenorenal, nonsuture	Serum alb. 4%, glob. 2.5% Bromsulf. retention 0.5 hr 10% Cephalin floc. 0	Marked improvement, subsidence of ascites; 1 yr postop. progressive gradual renal failure set in with rise in blood pressure and blood urea; passed tarry stools 1 14 mos. postop.; died of uremia 2 yrs. postop.; necropsy showed shunt to be closed
2	38, M	Painless jaundice, 16 yrs. before admission; anorexia, tiredness of 2 mos. duration; jaundice (recent); hematemesis	Atrophic, irregular nodular liver Esophageal varices Splenomegaly	Serum alb. 3.1%, glob. 4%, bilirubin 1.5 mg.%, phosphatase 6 B.U. Prothrombin time 70% of normal Bromsulf. retention 0.5 hr 60%	Pancytopenia	9/8/44 Splenorenal, nonsuture	Serum alb. 2.8%, glob. 3.2%, bilirubin 3 mg.% v., phosphatase 10 B.U.% Bromsulf. retention 0.5 hr 65%	Relief of ascites, gain in strength and weight for 9 mos. postop.; 11 mos. had recurrence of bleeding and died in liver failure; necropsy showed shunt had undergone fibrotic occlusion and was approximately 75% occluded
3	48, M	Cirrhosis secondary to prolonged common duct obstruction from calculus. Previous operations: cholecystojejunostomy, choledochogastrostomy	Splenomegaly Esophageal varices Ascites	Serum alb. 2.5% v., glob. 2.9% a, phosphatase 8.4 B.U.%, bilirubin 2.1 mg.% Bromsulf. retention 0.5 hr 20% Cephalin floc. neg.	Secondary anemia	11/11/44 Splenorenal vein graft, nonsuture	Serum alb. 3.4% v., glob. 2.2% av., bilirubin 1.9 mg.%, phosphatase 8.4 B.U.% Cephalin floc. neg.	Ascites and attacks of fever with jaundice cleared; bromsulf. retention (0.5 hr.) remained as high as 25 and 35% after injection, however; patient gained strength and weight but 1 yr postop. passed tarry stools; over 2.5 yrs. follow-up, 3 additional bleeding episodes but no return of ascites
4	39, M	Virus hepatitis complicated by sporotrichosis (subcutaneous) 3 mos. prior to first hematemesis	Jaundice Splenomegaly Esophageal varices Ascites	Serum alb. 2.4%, glob. 3.4%, bilirubin 4.8 mg.%, phosphatase 9.1 B.U.% Prothrombin time 50% of normal Cephalin floc. 4+	Secondary anemia Leukopenia	6/7/45 Portal vein to vena cava, end-to-side, nonsuture	6/9/45: Nonprotein nitrogen 136 mg.%	Second postop. day patient became comatose; died on third day; necropsy revealed an atrophic liver with coarse irregular nodular cirrhosis; there were areas of liver cell degeneration and periportal fibrosis with liver cell necrosis

continued

TABLE V (continued) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
5	48, M	Edema of legs and ascites for 3 mos.	Splenomegaly Ascites Laennec cirrhosis	Serum alb. 2.9%, glob. 3.3%, phosphatase 4 B.U.% Cephalin floc. neg. Bromsulf. retention 0.5 hr 35%	Secondary anemia Leukopenia	4/17/45 Portal vein to vena cava, end-to-side, nonsuture Portal pressure 390 mm. water	5/31/45: Serum alb. 3.9%, glob. 3%, phosphatase 3.3 B.U.%, bilirubin 1.5 mg.% Cephalin floc. 3+ 8/7/45 Bromsulf. retention 0.5 hr 20%	Patient gradually improved for 4 mos. and became ascites-free finally; convalescence punctuated with attacks of weakness, tremor, dizziness, and stupor; serum alb. averaged 2.1%, glob. 3.3% over this period; case followed carefully until death from liver failure 3/1/47 (nearly 2 yrs. postop.); serum alb. averaged 2.5%, glob. 3.1%; spleen remained palpable
6	50, M	Alcoholic history; intractable ascites; syphilis	Laennec cirrhosis Splenomegaly Esophageal varices	Serum alb. 2.4%, glob. 2.6%, bilirubin 0.7 mg.% Galactose removal constant, 2.2 Cephalin floc. 4+ Bromsulf. retention 0.5 hr 40%	Thrombocytopenia	9/28/46 Splenorenal, nonsuture	9/30/46 Serum urea nitrogen 74 mg.%	Patient did poorly during operation under ether anesthesia; abdominal distention promptly developed following operation with failure of blood pressure to rise to satisfactory levels during first 24 hrs. despite supportive measures; urinary output fell off on second day; urea nitrogen rose; patient died in coma on 4th postop. day
7	33, F	History of antiluetic treatment; mild jaundice for 8 yrs.; hematemesis	Splenomegaly Irregular nodular cirrhosis of liver Esophageal varices	Serum alb. 4.7%, glob. 1.5%, bilirubin trace, phosphatase 1.3 B.U.% Cephalin floc. neg. Prothrombin time 70% of normal Bromsulf. test normal	Pancytopenia	5/4/46 Portal vein to vena cava, end-to-side, suture Portal pressure before shunt 290 mm. water; after shunt 240	5/9/46: Serum bilirubin 2.8 mg.% 5/18/46: Serum alb. 4.2%, glob. 1.3%, bilirubin 1.7 mg.% phosphatase 3.4 B.U.% Cephalin floc. neg.	Esophagrams taken following operation showed complete disappearance of the varices; patient, who for 4 yrs. prior to operation had many hemorrhages, has had none now 2 yrs.; since operation the pancytopenia has not disappeared, and the spleen can sometimes be felt

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
8	28, F	Subject to ankle edema and hemorrhoids; sudden enlargement of liver with ascites 3 mos. previous; pleural effusion, right side	Hepatomegaly Acute passive congestion (biopsy) Congestive splenomegaly (mild) Ascites	Serum alb. 4.0%, glob. 2.8%, phosphatase 2.2 B.U % Cephalin floc. 2+ Bromsulf. retention 0.5 hr 30%	Secondary anemia (WBC 24,000)	3/6/46 Splenorenal, nonsuture Portal pressure 324 mm. water	5/10/46: Serum alb. 4% glob. 2.4% 5/23/46: Bromsulf. retention 0.5 hr 20% Cephalin floc. neg. WBC remained high (29,000); platelets 2,830,000	Diagnosis was considered to be thrombosis of hepatic veins; 3 wks. postop. ascites formation had been reduced by one-half but edema of legs and right pleural effusion persisted until sodium lactate and potassium acetate therapy was instituted; now 2 yrs. postop.
9	34, M	Alcoholism, ascites for 1 yr; edema of legs and scrotum	Jaundice Esophageal varices Extremely atrophic Laennec's cirrhosis Very slight splenomegaly	Serum alb. 3%, glob. 3% bilirubin 1.4 mg.-%, phosphatase 3 B.U %		2/18/43 Portal vein to right kidney vein, nonsuture		Technical death from hemorrhage due to failure to secure small omental vessel before closing the abdomen; patient died 2 hrs. after reexploration and securing the vessel (vein)
10	28, F	Jaundiced 1927; at operation enlarged liver; cicatricial tissue about common and cystic ducts; slight icterus persisted; 1938 cholecystectomy; choledochostomy; 1944 onset of hematemesis; icterus cleared	Splenomegaly Esophageal varices Liver biopsy periportal fibrosis	Apr 1944: Serum alb. 3.5% glob. 3% bilirubin 0.8 mg.% phosphatase 2.7 B.U % Cephalin floc. 4+ Bromsulf. retention 0.5 hr 25% Feb. 1947: Cephalin floc. neg. Bromsulf. retention 0.5 hr 13% Galactose removal constant 1.3	Pancytopenia	3/4/47 Splenorenal, nonsuture	9/10/47: Galactose removal constant 1.5	3 mos. postop. homologous serum jaundice developed during which time cephalin floc. became 4+, serum alb. 3.4%, glob. 3.4%, phosphatase 17.1 B.U %, and bilirubin 9.4 mg.%; after some 6 wks., jaundice cleared, cephalin floc. returned to normal; and on 8/28/47 serum alb. was 3.9% glob. 2.9%; patient gained weight and strength; no gastrointestinal bleeding since shunt was established

continued

TABLE V (*continued*) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
11	28, M	Hematemesis since age 15; splenectomy and liver biopsy diagnosis of liver cirrhosis, 1938 thereafter, platelet count became normal	Atrophic nodular liver Esophageal varices Ascites Enlarged (polycystic) right kidney	12/20/44 Serum bilirubin 1.9 mg.% Feb. 1945 Serum alb. 3 3%, glob. 5 2%, phosphatase 10.7 B.U %, cholesterol 493 mg.% Bromsulf. retention 0 5 hr 42% Cephalin floc. 3+ Hippuric acid excretion 1 hr 0 8 Gm.	Platelets normal Persistent secondary anemia Leukocytosis	3/2/45 Vein graft bridging of portal vein to vena cava, end-to-side, suture	10/3/45 Bromsulf retention 0.5 hr 40% Cephalin floc. 3+ Hippuric acid excretion 1 hr 1.5 Gm. 12/3/46 Serum alb. 2 1%, glob. 4 5%, phosphatase 16 B.U % 4/4/47 Cholesterol mg.% (verified), esters 253 mg.% 3/18/48: Serum alb. 1 5%, glob. 4 7% 6/4/48 Serum bilirubin 2 9 mg.%	Gain of 30 lbs. and freedom from ascites followed operation; patient felt well and over 3 yr period worked fairly consistently; 2 attacks of melena and 1 of hematemesis occurred during the period; liver chemistry was characterized by low serum alb., high glob., high cholesterol (though esters were in excess of 60% of total) elevated phosphatase; liver function declined progressively over 6 mo. period following pneumonia; died 6/8/48, apparently in liver failure; no necropsy
12	46, F	4 attacks of hematemesis year previous, one 3 mos. after splenectomy; no history of alcohol or hepatitis; 11/22/46, splenectomy and liver biopsy	Liver slightly enlarged biopsy periportal fibrosis Cholelithiasis, calculi in gallbladder Nephrolithiasis, left kidney Esophageal varices	11/21/46; Bromsulf. retention 0.5 hr 20% 2/14/47 Serum bilirubin 2.7 mg.%, alb. 3.9% phosphatase 12 9 B.U.% glob. 3 4% Cephalin floc. 3+ 3/26/47; Serum cholesterol—total 358 mg. %, ester 233 [illegible]	Secondary anemia	4/10/47 Proximal end of inferior mesenteric to vena cava, end-to-side, suture Portal pressure 350 mm. water	4/21/47; Serum alb. 4.3%, glob. 3 7%, cholesterol 305 mg.% Cephalin floc. 1+ 4/30/47 Serum alb. 4%, glob. 3 3%, bilirubin 1 6 mg.% Cephalin floc. neg. 9/17/47 Bromsulf retention 0 5 hr 20%	X-rays of esophagus 4/2/47 failed to show varices; patient feels well and has been free of hemorrhage since establishment of the shunt; has gained too much weight; now 1 yr 4 mos. postop.

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
13	40, F	Anorexia, lost 20 lbs. in 6 mos.; aversion to meats; pain in upper abdomen; occasional nausea and vomiting; alcohol intake considerable; first hematemesis 1 yr after start of liver dietary regimen; ascites persisted	Emaciated, jaundiced; Liver very large, tender; biopsy Laennec cirrhosis; Spleen moderately enlarged; Ascites; Esophageal varices	2/8/46 Serum alb. 3 4%, glob. 2 1%, bilirubin 2 8 mg.%, phosphatase 4 6 B.U %; Cephalin floc. neg.; Bromsulf. retention 0 5 hr 40%; 2/20/47 Serum alb. 3%, glob. 3 3%	Secondary anemia	4/18/47 Splenorenal, hemostat; 5/12/47 Portal vein to vena cava, end-to-side, suture; Necropsy 9/2/47 showed both shunts closed	4/21/47: Serum alb. 3.4%, glob. 3%; 4/18/47: Bromsulf. retention 0 5 hr 25%; 6/11/47 Serum alb. 3%, glob. 2 8%; 7/1/47: Serum alb. 3 6%, glob. 2 3%; 8/7/47 Serum alb. 3 4%, glob. 3 7%; After onset of hepatitis 8/22/47 Serum alb. 2 8%, glob. 3 4%, bilirubin 24 mg.%, phosphatase 6 B.U %	Though portal pressure was reduced from 340 mm. of water to 233 following establishment of splenorenal shunt, hemorrhage followed administration of albumin intravenously; under assumption that shunt was occluded, second operation was performed; during hospital stay patient received transfusions of plasma; was ascites free and doing well until 8/9/47 (113 days after splenorenal and 38 days after portal vein to vena cava shunt) when he suddenly developed homologous serum jaundice and died of liver failure 23 days later (9/2/47)
	43, M	4 attacks of gastrointestinal hemorrhage over 1.5 yrs. period; exposure to carbon tetrachloride; occasional drink of whisky; esophageal varices demonstrated by x-ray 1946	Spleen 2.5 times normal; Liver markedly nodular atrophic; Slight ascites; Esophageal varices	Serum alb. 3.1%, glob. 3 3%, phosphatase 3.9 B.U %, bilirubin trace; Cephalin floc. neg.; Bromsulf. retention 0.5 hr 6%	Pancytopenia	5/17/47 Splenorenal, suture; Portal pressure before shunt 320 mm. water; after shunt 235	6/13/47 Bromsulf. retention 0.5 hr 25%; 7/28/47 Bromsulf. retention 0.5 hr 20%; 10/21/47 Serum alb. 4 1%, glob. 3%; Cephalin floc. neg; Bromsulf. retention 0 5 hr none	Patient gained weight and strength following operation and resumed former occupation as electrician; most interesting feature of case was extreme apparent damage to liver in the gross with essentially normal liver function; portal pressure measured 320 mm. of water before shunt was opened, 235 after opening shunt; no further episodes of bleeding

TABLE V (continued) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
15	41 F	Jaundice (relatively painless) 7 yrs. duration; diet deficient (no meat) until 2 yrs. prior to admission for 4 yrs. prior to admission patient's course downhill with weight loss of 41 lbs. and bouts of ascites and jaundice with clay-colored stools; a massive hematemesis in April 1947; menorrhagia had been severe	Hepatosplenomegaly observed for 6 yrs. Esophageal varices	Dec. 1946 Wassermann 4+ Cephalin floc. 2+ Serum bilirubin 11 mg.%, phosphatase 21 B.U. % 6/9/47; Serum phosphatase 33 B.U %, alb. 3.4%, glob. 4.6%, bilirubin 0.8 mg.% Cephalin floc. neg. Prothrombin time 60% of normal Wassermann 4+ Kline 4+ Galactose removal constant 1.9	Secondary anemia Platelets 171,000	6/24/47 Splenorenal, suture Portal pressure 480 mm. water	7/30/47 Serum bilirubin 5.6 mg.% 8/8/47 Serum phosphatase 27 B.U % Cephalin floc. = Prothrombin time 70% of normal (without hykinone) 8/8/47 Serum alb. 2.6%, glob. 3.8% Galactose removal constant 2.4 8/25/47; Cephalin floc. 3+	Recurring subphrenic abscesses delayed return of liver compensation; on discharge, hykinone therapy was unfortunately discontinued and gastrointestinal bleeding secondary to hypoprothrombinemia developed; was readmitted 8/24/47 and died in coma; necropsy showed advanced biliary and portal cirrhosis, occlusion of the common duct with stones; splenorenal shunt was patent
16	37 F	1942, cholecystectomy exploration of common duct; same year operation for repair of common duct stenosis; 1944, anorexia and weakness; from Dec. 1946 to July 1947 8 severe attacks of hematemesis	Spleen enlarged 5 times normal Liver cirrhotic with small nodules Ascites	July 1947; Serum alb. 4%, glob. 1.8%		8/8/47 Splenorenal, suture (Belvyne) Portal pressure 410 mm. water	Dec. 1947; Albumin-globulin ratio reported as normal	12/15/47 (4 mos. follow-up) patient had gained 22 lbs.; no ascites or edema of legs; hb. 12 Gm., albumin-globulin ratio normal; 6/2/48 patient in perfect health, no ascites or edema; hb. 14.4 Gm., RBC 4,100,000, WBC 9,500, platelets 218,000; though intravenous pyelogram failed to outline kidney pelvis on the left, we believe splenorenal shunt is patent; no episodes of gastrointestinal hemorrhage over 11 mos. follow-up, compared to 8 attacks in 8 mos. preop.

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
17	13, F	Swelling in left side of abdomen [illegible] with occasional attacks of epigastric pain for 6 yrs.; 1 recent episode of hematemesis	Hepatomegaly Splenomegaly Esophageal varices Portal cirrhosis of liver (biopsy)	6/9/47: Serum alb. 3.4%, glob. 2.6%; phosphatase 16.5 B.U.%, cholesterol 140 mg.% Prothrombin time normal Bromsulf. retention 0.5 hr 8% Cephalin floc. 1+	Pancytopenia	6/14/47 Splenorenal, suture Portal pressure 390 mm. water	6/20/47: Serum alb. 4%, glob. 3%]	1 episode of hematemesis 11 mos. after splenorenal shunt; reoperated 8/1/48, portal pressure found to be 310 mm. water; an end-to-side portal vein to vena cava shunt was established
18	34, F	Jaundice through last third of pregnancy 7 and 4 yrs. respectively prior to admission; enlarged spleen 1.5 yrs.; "yellow" jaundice at age 7	Slight jaundice Hepatomegaly left lobe Spleen 2.5 times normal Portal cirrhosis of liver (biopsy) Varicose veins of legs Ulcer right leg	9/10/47: Serum alb. 3%, glob. 2.4%, bilirubin 2 mg.% Prothrombin time 80% of normal Cephalin floc. 4+ Thymol turbidity 4+	Pancytopenia	9/18/47 Splenic vein to vena cava, end-to-side, suture Portal pressure 600 mm. water		4/7/48 (7 mos. postop.) has gained 22 lbs.; no evidence of gastrointestinal bleeding; no ascites; varicose ulcer of right leg still present but improved; some ankle edema; easy fatigability; ankles swell intermittently
19	67 F	Treated for hypertension prior to admission; weakness of 3 mos. duration	Hepatosplenomegaly EKG left axis deviation Heart enlarged to right and left	4/23/47: Serum alb. 3.9%, glob. 2.4% Cephalin floc. 4+ Wassermann 4+ Kline 4++ Bromsulf. retention 0.5 hr. 20% Prothrombin time 80% of normal	Secondary anemia Leukopenia Platelets 130 000	5/9/47 Splenorenal, wire Portal pressure 240 mm. water		V. nous pressure became elevated on third postop. day; some hours later patient died suddenly of what was thought to be cardiac failure; no necropsy obtained, but pathologic diagnosis made on basis of liver and spleen biopsy was myeloid megakaryocytic hepatosplenomegaly

continued

TABLE V (continued) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
20	40, F	Hematemesis recurring 18 mo. intervals for 6 yrs. prior to admission	Spleen 6 times normal Liver grossly normal, but biopsy showed portal cirrhosis Esophageal varices	2/2/48 Serum alb. 5 1%, glob. 2 6%, phosphatase 2.3 B.U % Cephalin floc. 3+ Thymol turbidity 3+ Bromsulf. retention 0 5 hr neg.	Slight secondary anemia Slight leukopenia	2/5/48 Splenorenal, suture Portal pressure 490 mm. water	2/25/48 Bromsulf. retention 0.5 hr 7% Cephalin floc. 3+ Thymol turbidity neg.	4 mos. post. p. (6/2/48) patient symptom-free; no ascites; no edema of ankles; liver edge just palpable
21	54, M	3 hematemesis attacks from Aug. 1946; history of heavy alcohol intake; swelling of legs	Laennec cirrhosis of liver (atrophic hobnail) Spleen several times enlarged Legs swollen Obesity (280 lbs.)	10/18/47 Serum alb. 4.1%, glob. 2 4%, phosphatase 3 1 B.U % Cephalin floc. neg. Prothrombin time 80% of normal	Sedentary anemia Leukopenia	10/20/47 Splenorenal, suture	10/22/47 Serum alb. 3 6%, glob. 1 9%, nonprotein nitrogen 49 mg. % 11/7/47: Serum alb. 2 7%, glob. 2 6% nonprotein nitrogen 37 mg. %, bilirubin 3 7 mg. % Cephalin floc. 3+	Due largely to obesity patient had a prolonged anesthesia of nitrous oxide and pentothal; convalescence complicated by marginal liver failure and nitrogen retention, fortunately patient's appetite remained good; gradually improved; discharged to his home out of city on 28th postop. day; 2 weeks after discharge patient died of peritonitis secondary to perforated peptic ulcer (confirmed by necropsy)
22	33, M	Hepatosplenomegaly 6 yrs.; weakness for 3 yrs.; bleeding from nose, mouth, and in stool for 1 yr; treated for central nervous system lues in 1928-30; jaundice with swollen liver 25 yrs. previous to admission; intermittent swelling of ankles	Spleen 4 times normal Liver enlarged, nodular having appearance of Laennec's cirrhosis (no biopsy)	10/6/47 Serum bilirubin less than 1 mg.-%, phosphatase 3.1 B.U.-% Cephalin floc. 3+ Thymol turbidity 3+ Prothrombin time 80% of normal 2/16/48: Serum alb. 4.4%, glob. 3 2% Galactose removal ...	Hb 14 Gm. RBC 3,500,000 WBC 4,400 Platelets 44,000	2/6/48 Splenorenal, suture		Portal pressure measured only 230 mm. of water (128 mm. after opening shunt); has done exceedingly well since operation; 3/5/48, Hb. 16 Gm., WBC 8,250, platelets 162,000; no further bleeding; last examined 6/2/48, liver 3 fingerbreadths below rt. costal margin (unchanged); no ascites

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
23	47 F	Cholecystectomy for gallstones 1941, convalescence complicated by 9 days of jaundice; hematemesis started in July 1946 (4 attacks); swelling of ankles and abdominal fullness since Nov 1947	Spleen 5 times normal; Liver enlarged, surface finely granular; path. diagnosis, Laennec cirrhosis; Esophageal varices; No ascites	2/4/48: Serum phosphatase 4.4 B.U. %, alb. 3.9%, glob. 2.6%; Cephalin floc. 3+; Thymol turbidity 3+; Prothrombin time 75% of normal; Bromsulf. retention 0.5 hr 25%	Secondary anemia; Platelets 106,000	2/18/48 Splenorenal, suture		Severe bleeding tendency (clotting time 20 min.) throughout operation necessitated reparotomy because of subcapsular hemorrhage; persistent nose bleed about endotracheal tube resulted in accumulation of blood clots throughout bronchial tree which in turn caused extreme respiratory embarrassment from lung atelectasis; repeated bronchoscopy gave slight relief but laryngeal edema supervened necessitating tracheotomy on the 4th postop. day; by this time pulse and respiration were extremely high; temperature and W.B.C. rose; gastrointestinal bleeding ensued and despite transfusions patient died on 8th postop. day; necropsy showed marked collapse of lungs with edema; esophagus contained varices but a bleeding site was not lo-
24	18, F	Infectious hepatitis 1941; persistent slight jaundice with exacerbations; first hematemesis Nov 1945; ascites supervened and persisted for several months, from Oct. 1946 to May 1947 4 additional severe hemorrhages following some of which patient in semicoma for days	Slight jaundice; Spleen 4 times normal; Liver cirrhotic, markedly trophic; biopsy characteristic posthepatitic cirrhosis; Slight ascites; Esophageal varices	Serum alb. 3.5%, glob. 2.9%, bilirubin 1 mg. %, phosphatase 2.6 B.U. %; Thymol turbidity 11 units; Bromsulf. retention after 45 min. 23%; 5/1/47: Serum bilirubin 1.3 mg. %, phosphatase 6.1 B.U. % alb. 3.6%, glob. 2.7%; Prothrombin time 50% of normal; Cephalin floc. 3+	Severe pancytopenia	5/13/47 Splenorenal, suture; Portal pressure 480 mm. water	4/23/48 Serum alb. 2%; 5/?/48 Serum alb. 2.93%, glob. 3.1%, bilirubin 1.8%; Thymol turbidity 13 units; Gamma globulin 31 units; Total lipids 500 mg. %	Repeated hemorrhages (4 severe attacks of gastrointestinal hemorrhage during 5 mos. prior to admission) accompanied by progressively serious liver decompensation, often bordering on coma, was the preoperative status; since establishment of a splenorenal shunt, over 14 mos. follow-up, patient has been free of attacks of hemorrhage and ascites—the latter despite a progressive decline in serum albumin; patient has gained 24.5 lbs. since operation, feels well and attends college; swelling of legs, first noted 4 months post op. when she had gained 20 lbs., has been bothersome

cated; splenic vein appeared inflamed and filled with a 24 hr thrombus; anastomosis itself was patent

continued

TABLE V (*continued*) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
25	[illegible], F	Feeling of tiredness 5 yrs.; spleen known to be enlarged 1 yr.	Splenomegaly; Laennec cirrhosis (necropsy)	6/2/46 Serum alb. 3 [illegible]%, glob. 2.4%, bilirubin 1.5 mg. %, phosphatase 2.5 B.U %, cholesterol—total 1[illegible] mg. % free 36 mg. %, esters 12[illegible] mg. %; Cephalin floc. 4+; Bromsulf. retention 0.5 hr 24%; 9/2[illegible]/47: Prothrombin time 60% of normal	Pancytopenia	9/24/47 Splenorenal, suture; Portal pressure 400 mm. water	10/16/47: Serum alb. 3 4%, glob. 3%; Cephalin floc. neg.; Thymol turbidity 3+; 10/20/47: Serum bilirubin 1.4 mg %, phosphatase 10.4 B.U %; 10/13/47 Prothrombin time 75% of normal	On 23th postop. day patient developed low back pain and severe nonbloody diarrhea, accompanied by rising temperature and white blood count; stool cultures grew out B. Salmonella Tennessee; tender sausage-shaped mass appeared along left wall of rectum on 34th day; 1 week later diffuse abdominal pain with distension supervened; patient' condition grew progressively worse despite transfusions and chemotherapy; died on 45th postop. day; necropsy revealed peritonitis secondary to gangrenous perforation of descending colon; an abscess about an old septic thrombus of left hemorrhoidal vein, with thrombus extension into the mesenterics, splenic, and portal veins; gram-negative bacillus was recovered
26	[illegible], F	1944, anorexia, weakness, upper abdom. pain and ascites; put on cirrhosis regime, 1945; ascites persisted following saphenoperitoneal anastomosis; in ensuing year 2 button operations failed to relieve ascites	Atrophic Laennec cirrhosis; Splenomegaly; Cholelithiasis, calculi in cystic duct; Ascites; Pitting edema of legs	9/17/46 Serum phosphatase 10.2 B.U %, bilirubin faint trace, alb. 3.7% glob. 2.2%; Prothrombin time 60% of normal; Cephalin floc. 3+; Bromsulf. retention 0.5 hr 25%	Secondary anemia	10/10/47 Splenorenal, suture; Portal pressure before shunt 280 mm. water; after shunt 200	10/24/47 Serum alb. 4%, glob. 2%; 11/[illegible]/47 Cephalin floc. 3+; Thymol turbidity 3+	Ascites and leg edema cleared following operation; there was progressive gain in stamina such as patient had not known for years; "liver palms" disappeared; slow weight gain
27	[illegible], M	History of alcoholism and lues; ascites followed attack of gastroenteritis 5 mos. prior to admission; required frequent paracenteses; marked wasting of body soft parts	Atrophic Laennec cirrhosis; Ascites	4/20/45 Serum alb. 2.3%, glob. 3%, phosphatase 10.3 B.U %, bilirubin faint trace; Prothrombin time 60% of normal; Cephalin floc. neg.; Bromsulf. retention 0.5 hr 40%; Intra hippuric acid test 0.82 Gm. excreted in 1 hr	None	4/24/45 Portal vein to vena cava end-to-side, nonsuture; Portal pressure 380 mm. water	5/7/45 Serum alb. 2.6%, glob. 2.8%; 5/[illegible]/45 Intra hippuric acid test 0.82 Gm. excreted in 1 hr	Patient, who had 9 liters removed regularly [illegible] paracenteses prior to operation, had only 1 paracentesis on 8th postop. day at which time 3 liters of ascitic fluid were removed; now, more than 3 yrs. since operation, patient has remained ascites free, has gained greatly in strength, and nearly 50 lbs. in weight, has worked, and maintained an excellent appetite

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
28	29 M	Exploratory laparotomy May 1946 revealed atrophic nodular liver congestive splenomegaly; subsequently alteration in speech and tremor of legs and hands; first hematemesis spring 1947; failed to improve on medical regime	Liver extremely atrophic, nodular suggesting healed subacute yellow atrophy; Splenomegaly; Kayser-Fleischer rings; Coarse intention tremor ataxia; Esophageal varices	3/10/47: Serum alb. 3.8%, glob. 2.6%; Cephalin floc. 4+; Bromsulf. retention 0.5 hr 13%; 9/8/47: Serum alb. 3.6%, glob. 2.2%; Prothrombin time 60% of normal	Pancytopenia	9/10/47 Splenorenal suture; Portal pressure 418 mm. water	9/12/47 Serum alb. 3.4%, glob. 1.7%; 9/15/47: Serum alb. 2.6%, glob. 1.4%	Operation was complicated by excessive bleeding, but blood pressure was well maintained by transfusions; temperature rose to 104 F. on 1st postop. day; patient became comatose on 2nd day and had attacks of what appeared to be "sham rage," during which disruption of wound occurred; slight jaundice appeared and coma deepened; patient died on 6th postop. day; no necropsy; it was assumed that death was due to liver failure; of interest that serum albumin level was well maintained until the end
29	24, M	1930, catarrhal jaundice; 1942, pain about umbilicus, nausea, vomiting, followed by diarrhea; temp. rose to 103 F.; liver biopsy 1944 showed nodular cirrhosis; cholecystogram revealed nonfilling gallbladder; ascites several yrs.; prior to 1943 drank 1 or more pints of whiskey; some loss of weight and strength	Liver hard, nodular, somewhat enlarged; Spleen moderately enlarged; Esophageal varices, subsequently demonstrated by x-ray	8/1/44: Serum alb. 3.3%, glob. 3%; Cephalin floc. 4+; Icteric index 47; 11/21/44: Serum alb. 2.9%, glob. 2.7%, bilirubin 2.7 mg.%, phosphatase 9.5 B.U.%; Bromsulf. retention 0.5 hr 70%	Pancytopenia	11/23/44 Splenorenal, nonsuture; Portal pressure 240 mm. water	2/6/45 Serum alb. 3.6%, glob. 3.5%; Cephalin floc. neg.; 10/16/45: Cephalin floc. 4+; Bromsulf. retention 0.5 hr 28%; Intrav. hippuric acid excretion 0.9 Gm. in 1 hr; 12/4/47: Serum alb. 2.5%, glob. 3.4, phosphatase 5.9 B.U.%; Cephalin floc. 4+; Thymol turbidity 4+; Prothrombin time 55% of normal	3 mos. after discharge patient was operated upon for perforated duodenal ulcer; 3 mos. thereafter he had an attack of abdominal pain, chills, fever and jaundice; following recovery from this the patient was in fairly good health for nearly 2 yrs. during which he got married and held down a job; starting in May 1947 patient began having attacks characterized by abdominal pain, chills, and fever lasting 7 to 10 days and recurring at 4 to 6 wk. intervals; diarrhea sometimes present, and a tarry stool was passed twice; x-rays revealed presence of esophageal varices; a posterior wall duodenal ulcer was also present; review of his liver chemistry in Dec. 1947 showed progression of the cirrhosis—a very low serum albumin and severe hypoprothrombinemia; 3 mos. later (Mar. 1948) patient died during an attack of fever accompanied by gastrointestinal hemorrhage

continued

TABLE V (continued). Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
30	64, F	Enlarged spleen noted 17 mos.; hematemesis followed by tarry stools, generalized edema and ascites 6 mos. prior to admission, anorexia for 3 mos.; hypertension and slight exertional dyspnea for 10 yrs.	Liver contracted, nodular Congestive splenomegaly Esophageal varices	3/9/48 Serum alb. 4.6%, glob. 1.8%, phosphatase 3.3 B.U.%, bilirubin 0.7 mg.%, cholesterol—total 219 mg.%, esters 143 mg.% Cephalin floc. neg. Thymol turbidity neg. Bromsulf. retention 0.5 hr. 28% Prothrombin time 70% of normal Galactose removal constant 3.3	Pancytopenia	4/12/48 Splenorenal end-to-side, suture Portal pressure 430 mm. water	4/13/48 Serum alb. 4.3%, glob. 1.7% Bromsulf. retention 0.5 hr. 27% 4/22/48: Serum alb. 3.6%, glob. 2.1%, bilirubin 1 mg.%	Esophagrams taken 2 wks. postop. showed little if any evidence of varices; auricular fibrillation for few days postop.; phlebothrombosis developed in right leg; has gained too much weight since operation; no ascites, slight ankle edema of the right leg; no further attacks of hemorrhage
31	49, F	Attack of rt. up. quad. abdom. pain diagnosed as gallbladder disease 12 yrs. prior to admission; alcoholic history; 2 mos. history of attacks of epigastric pain, with nausea and vomiting; progressive swelling of abdomen (ascites); 2 attacks of hematemesis in 1946	Splenomegaly Laennec cirrhosis Ascites Esophageal varices Obesity	10/18/43 Serum alb. 2.8%, glob 2.7% Cephalin floc. 3+ 10/28/46 Serum alb. 3.3%, glob. 2.1% Bromsulf. retention 0.5 hr 25% 1/8/48: Serum alb. 3.3%, glob. 3.4% Cephalin floc. 4+ 3/17/48: Serum alb. 2.8%, glob. 2.4% Cephalin floc. 4+ Thymol turbidity 3+	Pancytopenia	4/6/48 Splenorenal, suture	4/21/48: Serum alb. 2.5%, glob. 3%	Some 12 days postop. nausea and vomiting developed; distention and abdominal pain became progressive; on 14th day some bright red blood passed ¦ stools; pulse rate rose; WBC rose to 29,000; patient became jaundiced and died in coma on 17th postop. day; necropsy revealed mesenteric thrombosis including portal vein and splenorenal shunt

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
32	45, F	Subject to "gallstone" attacks all her life consisting of nonradiating epigastric pain, nausea, and vomiting; onset of chronic jaundice and fatigue 8 yrs. prior to admission; cholotomy 5 yrs. before; admission revealed liver cirrhosis; hematemesis; ascites (1 yr.)	Splenomegaly Jaundice Partial atresia of common duct Liver enlarged; biopsy periportal fibrosis Ascites Esophageal varices	1/22/48: Serum phosphatase 18.6 B.U.%; bilirubin 27 mg.%, alb. 3.1%, glob. 3.3%, cholesterol 81% esters Cephal. floc. ± Thymol turbidity 3+ Prothrombin time 50% of normal	Pancytopenia	2/13/48 Portal vein to vena cava, end-to-side, suture Portal pressure before shunt 370 mm. water; after shunt 260	2/18/48 Serum alb. 3.6%, glob. 2.2% Prothrombin time normal 2/27/48: Serum phosphatase 15 B.U.% 3/1/48: Serum bilirubin 2 mg.% Cephalin floc. 3+ Thymol turbidity 3+	It is of interest that the spleen, which was 5 times normal size, after operation shrank to size which it could not be felt; on discharge on 24th postop. day platelets had risen only to 176,000 and some anemia was present; the jaundice became slightly more marked a few days after operation but had cleared considerably before discharge; a skin biopsy showed hyperpigmentation (melanin) but no pigmentation of the liver; ascites cleared rapidly after operation, and x-rays of esophagus showed complete disappearance of varices
33	49, M	Alcoholic history; prolonged treatment for lues; 7 mos. history recurring pain in rt. up. quad. of abdomen; jaundice; clay-colored stools 3 wks.; attacks of melena (2); hematemesis on admission	Liver enlarged, nodular; biopsy Laennec cirrhosis Spleen enlarged moderately Multiple gummas Urethral stricture Esophageal varices	8/13/47 Serum alb. 3.3%, glob. 1.9%, phosphatase 12 B.U.%, bilirubin faint trace Kline and Wassermann 4+ Steel gales 4+ Cephalin floc. neg. 8/22/47: Bromsulf. retention 0.5 hr, 20% 9/8/47 Serum alb. 4.8%, glob. 1% 10/10/47 Galactose removal constant 2	Pancytopenia	10/20/47 Splenorenal, suture Portal pressure 315 mm. water	10/24/47: Serum phosphatase 5.7 B.U.%, bilirubin 4 mg.% Cephalin floc. and thymol turbidity neg. 10/27/47 Serum alb. 3.1%, glob. 1.4% 11/12/47 Serum alb. 2.7%, glob. 1.4%	Patient finally proved to have cirrhosis of liver with severe portal hypertension secondary to syphilis of liver; succumbed probably to pulmonary embolism, some 5 months after establishment of splenorenal shunt; a few days after shunt operation, while on antisyphilis therapy patient had severe episode of gastrointestinal bleeding accompanied by ascites; following supportive therapy including use of esophageal balloon, he recovered and remained free of hemorrhages until his death
34	63, M	1944, lobar pneumonia treated sulfa drugs, headache and nausea resulting; operation for biliary disease, with jaundice and clay-colored stools persisting for 2 wks.; 1948, recurrent attacks of up. abdom. pain; fatigue; enlarged spleen	Liver enlarged, grossly cirrhotic; biopsy mild interstitial fibrosis Spleen 5 times normal Excessive lymphocytic infiltration (microscopy)	3/27/46 Serum alb. 4.1%, glob. 2.7%, phosphatase 14 B.U.% Prothrombin time 40% of normal Cephalin floc. 4+ Intrav. hippuric acid test 1.6 Gm. excreted in 1 hr Bromsulf. retention 5 min. 60%, 0.5 hr 10% Kline and Wassermann 4+	Pancytopenia	4/23/46 Splenorenal, suture Portal pressure 230 mm. water	10/2/46 Cephalin floc. 3+ Serum phosphatase 14 B.U. Wassermann and Kline 4+ 3/21/47 Prothrombin time 30% of normal Cephalin floc. and thymol turbidity normal Kline normal	This man has gained strength and weight since operation but his exact diagnosis remains equivocal. The enlarged liver appeared cirrhotic in the gross, and on microscopy showed marked lymphocytic infiltration with minimal interstitial fibrosis; enlargement of spleen seemed due primarily to flooding of sinuses with blood, with a great increase in pulp lymphocytes; left kidney likewise showed accumulation of lymphocytes with multiple microscopic cysts; the false positive serology was of interest

continued

TABLE V (continued) Abstract of 44 Cases of Portal Hypertension in Which Seat of Obstruction in Portal System Was Intrahepatic

Case No.	Age and sex	Pertinent history	Pertinent findings	Blood and liver chemistry (preoperative)	Blood dyscrasia	Type of portacaval shunt	Blood and liver chemistry (postoperative)	Comments
25	48, F	2 attacks of hematemesis and 3 episodes of tarry stools prior to admission starting in 1942; cholecystectomy 10 yrs. prior to admission without relief of rt. up. quad. soreness and intermittent pain; recent weight loss 16 lbs.	Laennec' cirrhosis of liver (atrophic hobnail) Spleen moderately enlarged Esophageal varices Slight ascites	2/20/45 Serum phosphatase 20 B U % bilirubin (faint) trace, alb. 3.2%, glob. 4.5% Cephalin floc. ± Bromsulf. retention 0.5 hr 40% 4/24/45: Serum alb. 4.2%, glob. 3.4% Cephalin floc. + Kline test 4+	Secondary anemia	5/3/45 Portal vein to vena cava, nonsuture	5/10/45 Serum bilirubin 1 mg.%, phosphatase 2.9 B U % Prothrombin time normal 5/16/45 Bromsulf retention 0.5 hr 10% 4/18/45 Serum alb. 3.5%, glob. 3.3% 6/2/45: Serum alb. 4.1%, glob. 2.8% 10/1/45 Bromsulf. retention 0.5 hr 20% Intrav. hippuric acid test 1.1 Gm. excreted in 1 hr 8/26/46 Serum alb. 3.7%, glob. 2.3% Cephalin floc. 2+ Bromsulf. retention 0.5 hr. 40% 2/11/47: Serum alb. 3.9%, glob. 2.6% 10/2/47 Serum alb. 3.7%, glob. 2.3% 5/6/48. Serum alb. 4.2%, glob. 1.1%, bilirubin 0.6 mg.% phosphatase 6 B.U % Prothrombin time 50% of normal 7/23/48: Serum alb. 3.3%, glob. 1.4%, bilirubin 1.3 mg.%, cholesterol esters 67% of total Cephalin floc. 3+ Thymol turbidity 3+	Patient did extremely well after operation; no hemorrhages or ascites; suddenly on 7/30/46 (some 14 mos. postop.) patient became drowsy and disorientated, on admission 164/88; was responsive but without recollection of previous 20 hrs.; neurologic impression was of an attack of cerebral spasm (vascular); laboratory findings: sedimentation rate 42 mm., hb. 15 Gm., RBC 4,800,000, WBC 6,900, platelets 164,000, urine neg., serum bilirubin 1.8 mg.%, spinal fluid proteins 28 mg. %, chlorides 722 mg.%; neurologic findings were characterized by clonic movements of left arm, hyperactive reflexes on both sides, exhaustible ankle clonus on left; such attacks recurred from time to time; actual cause of the episodes of loss of consciousness never explained satisfactorily, but neurologic pattern of Parkinson's syndrome became [illegible] and cause was thought to be cerebral arteriosclerosis; severe diabetes developed early in 1947; by spring 1948 (3 yrs. after establishment of portacaval shunt) patient's liver chemistry had deteriorated considerably; hospitalized during her last illness, she died in coma 7/23/48; portacaval shunt found patent at necropsy; there had been no postop. bleeding episodes, and esophagrams had revealed complete disappearance of varices

36	30, M	Raised in Puerto Rico; history of bouts of fever with jaundice; 3 attacks of hematemesis starting in 1947; patient had received years before fuadin for schistosomiasis	Liver slightly enlarged, irregular surface (fasciculated) somewhat increased consistency (operation) Splenomegaly Esophageal varices	7/1/47 Serum alb. 4.1%, glob. 3.1%, phosphatase 2.9 B.U.% Cephalin floc. 1+ Bromsulf retention 0.5 hr. trace Prothrombin time 70% of normal Icteric index 12 Galactose removal constant 1.5	Secondary anemia Leukopenia	7/7/47 Splenorenal, suture Portal pressure 435 mm. water	7/22/47 Cephalin floc. neg. 8/8/47 Bromsulf. retention 0.5 hr 8% Galactose removal constant 3.2 Prothrombin time normal	3 mos. postop. anorexia, abdominal pain, and fever developed; liver became enlarged, and jaundice ensued; laboratory findings: cephalin floc. 4+ thymol turbidity 4+ serum bilirubin 6 mg.%, alb. 4.2%, glob. 4.4%; jaundice subsided and homologous serum hepatitis was diagnosed; patient was well until 6/10/48 (11 mos. postop.) when he had an attack of hematemesis; 7/26/48 patient was reoperated upon, and a side-to-side anastomosis effected between large vein in falciform ligament and vena cava; patient died of shock on 2nd postop. day; necropsy revealed hemorrhage to be from the anastomosis
37	43, M	Alcoholic history; antiluetic therapy 1935–37; progressive loss of weight since 1943; anorexia 5 mos.; jaundice 6 wks.; enlarged liver noted 1943, diagnosis of cirrhosis made; hematemesis	Liver nodular (operation); periportal cirrhosis (biopsy) Spleen 6 times normal Esophageal varices	10/12/46 Serum bilirubin 2.5 mg.% alb. 4.7%, glob. 2.1% Cephalin floc 4+ Bromsulf retention 0.5 hr 25%	Pancytopenia	1/20/48 Splenorenal, suture Portal pressure 333 mm. water	1/29/48 Serum alb. 4%; glob. 2% 7/20/48: Serum alb. 3.9%; glob. 2.8%	Of extreme interest in this case is finding of metastatic carcinoma in lymph node removed from hilar region of spleen at time of portacaval shunt procedure; repeated gastrointestinal x-rays had been negative; there have been no further episodes of gastrointestinal bleeding; but a recent (7/20/48) x-ray of abdomen reveals pressure defect along greater curvature of stomach which has been interpreted as possible carcinoma of pancreas; there has been no increase in serum bilirubin
38	32, M	Hepatitis with jaundice 1943; jaundice persisted; hematemesis with ascites recurring since April 1947	Hepatosplenomegaly Jaundice Esophageal varices Ascites (mild)	Serum alb. 2.9% glob. 3.8% Cephalin floc. 2+		1/26/48 Splenorenal, suture	July 1948: Serum alb. 2.9%; glob. 3.6%	Deeply jaundiced patient with severe posthepatitic cirrhosis had failed to improve under prolonged medical regime; splenorenal shunt established in Jan. 1948; after stormy convalescence ascites cleared and jaundice improved; no further bleeding episodes; recent follow-up visit revealed considerable improvement of patient

continued

Tumors of Bone

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Introduction

In recent times due to the joint efforts of the clinician, the pathologist, the roentgenologist, the biochemist, the biophysicist, and the research worker our knowledge of neoplastic diseases of bone has been considerably expanded. Prior to the advent of the microscope the physician was practically unable to distinguish the benign from the malignant tumor of bone, or either of these from a number of non-neoplastic diseases of bone. With the growth of our knowledge of pathology came a marked improvement in this regard and with the advent of the roentgen rays an additional diagnostic—and even therapeutic—agent of immeasurable importance was added. All this has been augmented in recent years by the science of biochemistry

It is the writers purpose to outline as fully as possible in the space allotted the present status of our knowledge of the diagnosis the treatment and the prognosis of tumors of bone and closely associated lesions, with due emphasis upon the more recent advances.

In order to gain a clear conception of the subject as a whole it is essential to understand the descriptive terms by which the various entities are known this in turn calls for a tabulated classification. While as yet none has been proffered that has proved satisfactory to all authorities in this field, the classification of the Bone Sarcoma Registry of the American College of Surgeons revised by Ewing in 1939 is undoubtedly the most widely accepted (Table I)

TABLE I Classification of Bone Tumors (after Ewing)

Malignant	Benign
Fibrosarcoma of bone	Nonosteogenic fibroma of bone
	Fibrous dysplasia
Osteogenic sarcoma	Osteoma
	Osteoid osteoma
	Exostosis
Primary chondrosarcoma	Chondroma
Secondary chondromyxosarcoma	Benign chondroblastoma (Codman's epiphyseal giant cell tumor)
Malignant giant cell tumor	Benign giant cell tumor
	Unicameral bone cyst
Endothelioma (angioendothelioma diffuse, Ewing's)	Cavernous angioma
	Plexiform angioma
Angiosarcoma	—
Myeloma (plasma cell myeloma myelocytoma erythroblastoma lymphocytoma)	—
Reticulum cell sarcoma	—
Liposarcoma	—

Diagnosis

It is important to arrive at a correct diagnosis in the early stages of a bone tumor in order to insure prompt and proper treatment. This is not always easy to accomplish for the following reasons too often the first physician consulted fails even to suspect the possibility of a malignant tumor and treatment is prescribed under the assumption that *some comparatively trivial condition exists*. Seldom is a roentgenogram taken at the first examination In fact, months of treatment with liniments physiotherapy and medication may intervene before films are ordered. The most important single objective in the campaign for earlier diagnosis is to make the profession realize the need of suspecting the possible presence of a bone tumor whenever pain in a limb persists for which no definite cause is apparent. This suspicion, once aroused should be the signal for an immediate, adequate roentgenographic examination. To be truly effective these measures ought to have the additional support of publicity so that the laity may be educated to appreciate the urgent need of prompt medical attention for deep-seated pain in a bone, *just* as women in general have come to realize the import of a lump in the breast.

HISTORY AND PHYSICAL EXAMINATION

A carefully elicited history and a searching and complete physical examination are still the foundation stones upon which all other

diagnostic measures must rest Their importance although frequently ignored cannot be overemphasized Failure to recognize this has resulted in serious errors both in the interpretation of roentgenograms and in the carrying out of laboratory tests



Fig. 1 Osteogenic sarcoma of lower end of femur Note obliteration of surface contours, swelling, moderate skin changes and position of optimum comfort in slight flexion.

Unquestionably realization on the part of the practitioner that pain in an extremity calls for a presumptive diagnosis of *sarcoma* and an immediate diagnostic survey is the most important single factor in arriving earlier at a correct diagnosis Such an attitude of suspicion would eliminate the interval of weeks or even months during which many patients receive treatment for "rheumatic" "muscular" or "neuritic" conditions consisting of massage heat, topical applications exercises and the like Authorities have insisted for years that persistent pain in a limb for which there is no obvious explanation is most often due to a bone tumor

Table II gives the suggested outline of a complete diagnostic survey which should be made when a bone neoplasm is suspected

TABLE II

Outline of a Complete Diagnostic Work Up

(1) *History* This should be complete including
  (a) Chief complaint { pain, its character and whether nocturnal; swelling; disability }
  (b) Onset of symptoms Sudden insidious, progressive intermittent
  (c) Previous illnesses
  (d) Accidents or injuries How when, where
  (e) Family history

(2) *Physical examination*. This should be thorough and include
  (a) General
    1 Primary tumor in breast, thyroid, kidney prostate etc
    2 Evidence of deformity of skull or long bones, neurofibromatosis, pigmentation, lymphadenopathy splenomegaly anemia
  (b) Local
    1 Inspection Swelling, deformity color of skin, presence of tumor and its location in respect to part of bone involved (Fig 1)
    2 Palpation Presence of tumor, its mobility, consistence (hard, soft elastic fluctuant pulsating) outline (discrete indefinite)
    3. Mensuration Circumference of limb at measured levels as compared with normal limb length and width of tumor

(3) *Roentgenographic examination* This should be both local and general. Spot films of involved bone in several projections and with varying degrees of intensity of exposure are valuable
  (a) Local Views of affected area in anteroposterior and lateral projections on films large enough to cover a wide area proximal and distal to area complained of or to site of any obvious tumor
  (b) General
    1 Chest anteroposterior and lateral views, for evidence of pulmonary metastasis
    2 Other bones, especially skull pelvis, spine humeri, and femurs

(4) *Laboratory studies* These should include
  (a) Routine blood count
  (b) Urinalysis including test for Bence-Jones protein
  (c) Serology
  (d) Blood chemistry
    1 Calcium, phosphorus, and alkaline phosphatase (also acid phosphatase if cancer of prostate is suspected) in serum
    2 Protein in serum if plasma cell myeloma is a possibility
  (e) Biopsy
    1 Aspiration biopsy
    2. Open biopsy if aspiration biopsy is unsuccessful or if it is considered inadvisable because of location of tumor or unwillingness by pathologist to render an opinion on aspirated material

ROENTGENOGRAPHIC EXAMINATION

While admitting that great assistance is rendered the clinician by an experienced roentgenologist's interpretation of the films of a bone lesion one must recognize that difficulties are encountered in

differentiating some of these conditions and that at times an accurate opinion based solely on the roentgenogram is impossible.

Table III may be helpful in making a roentgenographic diagnosis

BLOOD CHEMISTRY IN BONE NEOPLASMS*

There are several chemical tests which are of value in the study of bone disease Most of them are not highly specific for any one bone disorder and a brief consideration of bone metabolism is necessary in order to understand the significance of chemical changes

Bones are composed of secondary and tertiary calcium phosphate calcium carbonate and calcium hydroxide as mixed salts of varying proportions embedded in an organic matrix. The rigid bone structure contains blood vessels and encloses the marrow cavity Disorders commonly classed as bone diseases may originate in the cortex, the blood vessels or the marrow and give rise to chemical changes which differ with the tissue of origin.

The calcium and phosphorus of the bones are derived ultimately from the food In the normal individual they are absorbed from the gastrointestinal tract and transported by the blood stream to the bones Their deposition in the bone is aided by the enzyme, alkaline phosphatase *This enzyme is elaborated by the osteoblasts and* splits organic phosphorus compounds to give a local excess of phosphoric acid for deposition as calcium phosphate Calcium and phosphorus liberated from the bones in the course of normal catabolism are returned to the blood stream and excreted to some extent by the intestines but mainly by the kidney If the dietary intake of these elements is inadequate or if absorption is impaired as in vitamin D deficiency or chronic diarrhea, rickets results in the child and osteomalacia in the adult The latter causes changes in the bone the roentgenographic appearance of which is sometimes similar to that produced by primary bone disorders such as plasma cell myeloma The chemical changes however are different and will often afford a clue as to the differential diagnosis

Only about half of the calcium in the blood plasma is present in the ionized form. The remainder exists as a loosely bound compound with protein. The level of ionized calcium is raised by the

* Data supplied by Helen Q Woodard, Memorial Hospital

TABLE III

Differential Diagnosis of Bone Tumors, with Particular Reference to the Roentgenogram

Actual diagnosis	To be differentiated from
Osteogenic sarcoma	Endothelioma. When wide extent of shaft, especially midportion, is involved. Giant cell tumor When tumor is purely osteolytic and area of destruction is confined to epiphyseal area (site of giant cell tumors) Liposarcoma. This tumor is extremely infrequent a roentgenographic distinction may be very difficult. Inflammatory bone lesions (sclerosing and low grade subacute osteomyelitis) Ossifying hematoma (myositis ossificans) Unless stereoscopic views are taken that show process to be unconnected with shaft of bone and cortical line to be intact. Metastatic carcinoma. When lesion is apparently solitary it may resemble osteolytic sarcoma. Chondroblastoma (Jaffe) calcifying chondromatous giant cell tumor (Codman) Differentiation is difficult, and must depend ultimately upon biopsy Reticulum cell sarcoma When an osteogenic sarcoma is of osteolytic type, histologic examination may be necessary to establish the correct diagnosis. This is particularly true of lesions involving the metaphyseal area those occurring in the midshaft are more likely to prove to be reticulum cell sarcoma.
Endothelioma	Subacute osteomyelitis. A most difficult differential diagnosis to make Histologic proof should be obtained *before* any roentgen therapy is given in any doubtful case, otherwise a "false negative" result may often be obtained by biopsy and the malignant nature of the tumor recognized only at a later date Osteogenic sarcoma. *See below* under Osteogenic sarcoma. Reticulum cell sarcoma Differential diagnosis may be very difficult if the patient is below 30 years of age. Reticulum cell sarcoma occurs at any age endothelioma is confined to childhood and early adult life.
Giant cell tumor	Bone cyst Site, age of patient, and clinical course are different. Malignant type from Benign type. Generally the malignant form is a transition from a previously benign giant cell tumor A recurrence of activity during or after treatment should suggest that the lesion is undergoing malignant transformation. Tumors that are malignant from the outset are rare the roentgenographic features in such tumors are often more typical of a malignant central sarcoma than of a benign giant cell tumor Calcifying chondromatous giant cell tumor (Codman) chondroblastoma (Jaffe) These more closely resemble an osteogenic sarcoma, but may occasionally suggest a giant cell tumor. The tumors are benign. A biopsy is needed to establish the diagnosis Osteogenic sarcoma *See below* under Osteogenic sarcoma.

TABLE III (*Concluded*)

Actual diagnosis	To be differentiated from
Chondrosarcoma	Chondroma. May require expert microscopic examination for diagnosis. Small bits of tissue are insufficient material upon which to base an opinion. Giant cell tumor. Central chondromyxosarcoma may closely simulate giant cell tumor. This explains why in some cases of supposed giant cell tumor the results of radiation therapy given without histologic confirmation of the diagnosis, are discouraging. Osteogenic sarcoma. In children or young adults, differentiation from chondroblastic sarcoma may be extremely difficult. However distinction is not important, for the treatment is the same for both and the outlook is equally grave. Chordoma. This tumor is rarely seen. It may resemble sacral chondrosarcoma. The microscopic appearance of chordoma, however, is distinctive.
Plasma cell myeloma	Metastatic carcinoma. When evidence of a primary carcinoma is absent, differentiation is often impossible without histologic examination. Aspiration biopsy of one of the lesions, or sternal marrow puncture, may disclose the presence of plasma cells, thus leading to a correct diagnosis.

parathyroid hormone by mechanisms which are poorly understood. Parathyroid hormone also lowers the renal threshold for inorganic phosphorus. Excess parathyroid hormone thus promotes the excretion of both calcium and phosphorus, and may lead to depletion of these elements in the bones.

The alkaline phosphatase which is produced by the bones usually enters the blood stream readily, and is excreted by the liver. When liver function is impaired, the alkaline phosphatase may accumulate in the blood *instead* of being excreted. When liver function is normal, the level of alkaline phosphatase in the blood serum is a good indication of the extent of osteoblastic activity. It is increased (*1*) when the bones are *growing normally*, as in children, (*2*) when they are growing abnormally, as in osteitis deformans, (*3*) when rapidly growing tumors are present in bone, as in osteogenic sarcoma, or (*4*) when there is an attempt *to repair damage to bone*, as in hyperparathyroidism and some types of metastatic disease of bone.

Another enzyme, acid phosphatase, is elaborated in large quantities by the prostate gland and in small *quantities* by some other organs. Small amounts of acid phosphatase of unknown origin are normally present in the blood serum. Normally the acid phosphatase of the prostate gland does not enter the blood stream, *but it* usually

occurs when a carcinoma of the prostate has ruptured its capsule and spread to regional or distant sites. For this reason, determinations of the acid phosphatase in the serum are often useful in distinguishing metastases to bone of carcinoma of the prostate from such conditions as osteitis deformans which they may resemble roentgenographically

A portion of the protein in the blood serum is normally synthesized *in the bone marrow In certain diseases of the* bone marrow such as plasma cell myeloma, types of protein are produced which are abnormal in their properties and excessive in amount. The presence of one of these abnormal forms, Bence-Jones protein, in the urine, or a marked increase in the total protein of the serum, helps to confirm the diagnosis of plasma cell myeloma.

Primary Bone Tumor

Benign localized overgrowths of bone (chondroma osteochondroma, osteoma, exostosis) are characterized by slow growth of tissue not differing chemically from normal bone, and produce no deviations from normal in the blood chemistry

Solitary bone cysts cause no changes in the blood chemistry unless they are local manifestations of hyperparathyroidism.

The tissue of giant cell tumor itself contains negligible amounts of alkaline phosphatase but the injury caused by the tumor to adjacent uninvolved bone may result in a slightly increased production of alkaline phosphatase by that tissue Hence, benign giant cell tumors usually cause no changes in the blood chemistry if they are *aggressive or definitely malignant, however the defense* reaction set up in the surrounding bone may be sufficient to cause small elevations in the serum alkaline phosphatase.

Chemical changes produced by Ewing's tumor are similar to those produced by giant cell tumor and for the same reasons. Ewing's tumor is principally a *disease of children. The alkaline phosphatase* in the serum of children varies widely in accordance with the rate of growth of the normal bones. Changes in serum alkaline phosphatase produced by Ewing's tumor are likely to be considerably less than those produced by normal variations in the rate of growth of the body as a whole Little information therefore, can *ordinarily* be obtained as to the progress of Ewing's tumor in a child from determinations of the alkaline phosphatase of the blood serum.

In osteogenic sarcoma the tumor tissue may produce alkaline phosphatase in amounts ranging from that found in normal bone to over 100 times as much as in normal bone The alkaline phosphatase in the tumor usually enters the circulation readily, but some times does not. Hence in a patient suspected of having osteogenic sarcoma, the presence of normal serum alkaline phosphatase read ings does not disprove the diagnosis, but the presence of very large amounts of alkaline phosphatase in the serum lends considerable support to the diagnosis In patients with high values for serum alkaline phosphatase before treatment, effective radiation therapy or com plete surgical extirpation is followed promptly by a drop of the serum alkaline phosphatase to normal When the phosphatase does not fall to normal within 2 weeks after amputation residual disease is probably present. The development of metastases from osteogenic sarcoma is often, but not always associated with a rise in the serum alkaline phosphatase.

Data are lacking on the alkaline phosphatase content of tumor tissue in reticulum cell sarcoma of bone. In the serum of patients suffering from reticulum cell sarcoma the increases in alkaline phosphatase activity are small and inconstant

None of the above primary tumors of bone are associated with abnormalities in the calcium or inorganic phosphorus of the serum A child with a bone tumor may also have rickets The high serum alkaline phosphatase due to rickets should not be confused with that due to osteogenic sarcoma. In rickets, either or both the calcium and inorganic phosphorus of the serum are low while in osteogenic sar coma both are normal.

Metastatic Cancer of Bone

The process of metastasis to bone of cancer of soft part origin con stitutes a special type of bone injury Ordinarily bone responds to injury with an increased production of alkaline phosphatase to facili tate repair When bone thus responds to the injury caused by metastatic cancer foci, an increased amount of alkaline phosphatase appears in the serum and new bone is laid down unless the tumor is growing so rapidly as to outstrip the repair process (In the presence of such osteoplastic metastases the calcium and inorganic phosphorus in the serum remain unchanged) In most types of metastatic bone cancer the phosphatase response is lacking or slight, the metas-

tases are osteolytic and there is usually no change in the blood chemistry. When, however, osteolytic metastases are growing very rapidly the bone is destroyed at such a rate that the kidneys cannot excrete the liberated calcium and inorganic phosphorus, and they accumulate in the blood. The presence of hypercalcemia associated with osteolytic bone metastases always indicates a poor prognosis, and may be fatal in itself.

The great majority of osteoplastic metastases arise from cancer of the prostate. In most cases the tumor tissue growing in the bones continues to elaborate its characteristic enzyme, acid phosphatase; this escapes into the circulation and may be identified in the serum. In patients with metastatic disease of bone, the presence of an elevated serum acid phosphatase is almost certain proof that the disease is of prostatic origin. Nevertheless, absence of such an elevation does not exclude this diagnosis.

The rise in the serum alkaline phosphatase which occurs in some types of metastatic bone disease does not correspond to the extent of the disease but does correspond to the intensity of the repair reaction. Certain types of endocrine therapy apparently stimulate the regenerative capacity of bone, while roentgenotherapy diminishes it. That is the reason why the changes in the serum alkaline phosphatase of patients with metastatic disease of bone during therapy do not bear a close relation to the effect of treatment on the tumor although they do give some indication of the effect on the surrounding bone.

There are several nonmalignant diseases of bone which may have a roentgenographic appearance similar to that of metastatic cancer. In some of these the chemical findings are useful in establishing the differential diagnosis. *Osteitis deformans* is characterized by excessive production of alkaline phosphatase by bone, with the formation of abundant, poorly organized new bone. In this disease, the serum alkaline phosphatase is markedly elevated, the degree of elevation corresponding to the extent and activity of the disease. There is no significant increase in the serum acid phosphatase, and this serves to distinguish osteitis deformans from metastases to bone from carcinoma of the prostate.

Osteomalacia in the adult is the analogue of rickets in the child and gives rise to the same changes in blood chemistry. It may cause

bone changes similar in roentgenographic appearance to osteolytic bone metastases. But in osteolytic bone metastases there is seldom a significant rise in the serum alkaline phosphatase and there may be an increase in the serum calcium and inorganic phosphorus, while in osteomalacia the alkaline phosphatase is definitely elevated and either or both the calcium and inorganic phosphorus are below normal

Plasma cell myeloma is primarily a disease of the bone marrow but the presenting symptoms are usually due to the weakening of the osseous structure by overgrowth of marrow tissue This results in destruction of bone in the same way as does growth of metastatic carcinoma deposits In plasma cell myeloma as in osteolytic meta static disease the serum alkaline phosphatase is normal or slightly elevated while the serum calcium and inorganic phosphorus are often definitely elevated and may be very high As explained above, the total serum protein is definitely above normal in about half the cases of plasma cell myeloma and hyperproteinemia when present, will serve to distinguish plasma cell myeloma from metastatic carci noma of bone

In hyperparathyroidism, the normal action of the parathyroid hormone in lowering the renal threshold for inorganic phosphorus and raising the level of ionized calcium in the blood is accentuated. This leads to an increase in the urinary excretion both of calcium and phosphorus with possible stone formation. If the dietary intake is insufficient to compensate for the urinary loss calcium and phosphorus are withdrawn from the bones The bones respond to this in jury with an increased production of alkaline phosphatase but the increase though often marked is usually insufficient to conserve phosphate and prevent osteolysis Thus in the typical case of hyper parathyroidism there are osteolytic bone lesions kidney stones high values for serum calcium and alkaline phosphatase and low in organic phosphorus This syndrome is pathognomonic for hyperpara thyroidism. It is important to remember that the bone lesions of hyperparathyroidism may be solitary may roentgenographically resemble giant cell tumor or epulis and may show giant cells on microscopic examination of curetted tissue In such cases a careful study of the blood and urine chemistry will establish the true nature of the disease.

Differential Diagnosis

When all the evidence is in hand and *a bone lesion or disease process* has been proved to be present the diagnosis can most safely be reached by a process of exclusion. We have found the following procedure to be helpful (*1*) One decides whether the lesion under consideration is a tumor or not. (*2*) If it is believed to be a tumor one questions whether it is *benign or malignant and if the latter,* whether it is primary or metastatic Further steps in arriving at the diagnosis are suggested in the diagram shown in Table IV

Biopsy

Surgical biopsy is still the standard method of obtaining tissue for a histologic examination *Closure of the biopsy wound in layers with out drainage* has now been widely accepted as a cardinal principle Furthermore sufficient tissue from a truly representative area of disease must be submitted to the pathologist for a comprehensive *study and report. As a general rule, the biopsy should be per* formed by the surgeon who is to have the subsequent care of the case, should the condition prove to be one of tumor

ASPIRATION BIOPSY

*Aspiration biopsy has not been so widely adopted as its propo*nents could wish Micotti (57) was apparently the first to perform a successful aspiration biopsy when in 1922 he inadvertently obtained a small piece of tissue while aspirating what he believed to be a cyst, and a diagnosis of chordoma was made as a result. The success of this method at *Memorial Hospital* where *Martin and Ellis* (58) in troduced it in 1930 has been noteworthy Others have adopted it with satisfactory results. However it requires considerable experi ence and skill on the part of the pathologist and it has not as yet received the recognition it deserves from most clinicians

The advantages *of aspiration biopsy are* (*1*) *simplicity of tech* nic making it suitable for outpatient clinic or admitting department, (*2*) promptness with which a report can be obtained (15 to 30 min utes (*3*) economy saving the hospital admission and charges for operating room anesthesia and the like (*4*) possibility of immediate definitive treatment, *either surgery or roentgenotherapy*

The disadvantages of aspiration biopsy are (*1*) Failure in some cases to obtain tissue (*2*) failure on the part of the pathologist to

TABLE IV

Differential Diagnosis by Exclusion in a Case of Bone Lesion

TUMOR

- Benign
  - Central
    - Chondroblastoma (Jaffe)
    - Chondroma
    - Myxoma
    - Nonosteogenic fibroma (Jaffe)
    - Bone cyst
    - Giant cell tumor benign
    - Xanthoma
  - Central and cortical
    - Angioma of bone
    - Osteoid osteoma
    - Multiple chondrodysplasia (Ollier's disease)
  - Cortical
    - Exostosis
    - Osteochondroma
- Malignant
  - Primary
    - Monostotic
      - Osteogenic sarcoma
      - Endothelioma (Ewing's sarcoma)
      - Reticulum cell sarcoma
      - Liposarcoma
    - Polyostotic
      - Plasma cell myeloma
      - Myelocytoma
      - Erythroblastoma
      - Lymphocytoma
  - Metastatic
    - Breast
    - Kidney
    - Thyroid
    - Prostate
    - Lung
    - Other sites

NOT A TUMOR

- Inflammatory
  - Pyogenic (Brodie's abscess)
  - Syphilis (Yaws)
  - Tuberculosis
  - Chronic sclerosing osteitis (Garré)
- Posttraumatic
  - Myositis ossificans
- Parasitic
  - Hydatid disease of bone
- Granulomatous
  - Letterer-Siwe disease
  - Hand-Schüller-Christian disease
  - Eosinophilic granuloma
- Lipid Storage
  - Niemann-Pick disease
  - Gaucher's disease
- Circulatory
  - Calcinosis
  - Aseptic necrosis (caisson disease)
- Endocrine
  - Hyperparathyroidism (Recklinghausen's disease)
  - Acromegaly
- Uncertain Etiology
  - Paget's disease (osteitis deformans)
  - Fibrous dysplasia
  - Melorheostosis
  - Osteopetrosis
  - Osteopoikilosis
  - Spontaneous absorption of bone (phantom clavicle)

identify cells obtained in some cases (3) possibility of creating a situation favorable to metastasis because of intratumoral hemorrhage (4) possibility of implanting viable tumor cells along the needle tract.

We have little evidence that the two last mentioned are real dangers since dissemination and tumor implantation that could be attributed to the aspiration biopsy have never been observed by us.

Technic of Aspiration Biopsy

The more deeply situated the tumor the more difficult it may be to select the site for aspiration Another factor to be considered is whether the tumor is centrally located and surrounded by an intact shell of bone For example in aspirating a tumor of the neck of the femur in which roentgenograms showed the cortex to be broken on the superior surface care in placing the limb in the proper position and in directing the angle of the needle made the procedure relatively simple and resulted in a diagnosis of osteogenic sarcoma. To expose this region for surgical biopsy is of course a major procedure.

For those not acquainted with the technic we quote from Martin and Ellis (56)

"The special paraphernalia required is an ordinary 18-gauge needle 5 to 10 cm in length (which should be new and sharp) and a 20 cc Record syringe. For the preservation of the specimen, glass slides and a specimen bottle with 10 per cent formalin are needed. (Fig. 2)

"The skin at the site of the intended puncture is painted with iodine and a small area of skin infiltrated with 1 per cent novocaine. With a bistoury pointed scalpel (No. 11 Bard Parker blade) a minute stab wound is made through the skin with the instrument held at right angles to the skin surface. This puncture of the skin facilitates insertion of the needle An 18-gauge needle attached to a tightly fitting Record syringe is then inserted and advanced slowly through the superficial tissues until the point is felt to enter the suspected neoplastic mass. Guided by palpation with the disengaged hand, it is striking how readily a difference in consistence of the tissues can be felt as the needle enters a mass of neoplasm When the point of the needle is felt to enter the tumor the piston of the syringe is partly withdrawn so as to produce a vacuum and the needle slowly advanced 1 to 3 cm depending on the anatomy and size of the tumor Maintaining the vacuum, the needle is then withdrawn to the same distance and advanced again. This manipulation may be repeated two or three times at the discretion of the operator care being taken to maintain the vacuum when the needle is advanced or withdrawn. Aspiration with the needle at rest is not sufficient to draw tissue into the needle in most cases By advancing the needle and aspirating simultaneously a plug of tissue is both forced and drawn into the needle Maintaining

suction during partial withdrawal detaches the plug of tissue already within the needle. We have found this detail to be very essential. Before the needle i completely withdrawn from the tissue the piston must be slowly released until the pressure in the needle is equalized or better still, the syringe detached and th needle withdrawn separately otherwise the aspirated

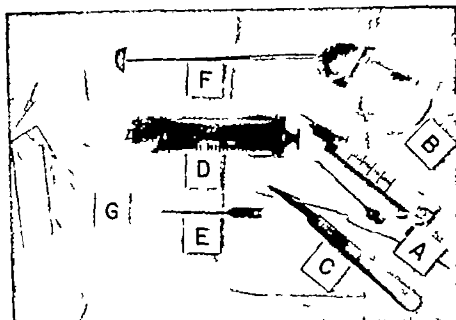


Fig. 2. Setup for aspiration biopsy A 5 cc hypodermic syringe and needle note longer needle for deep infiltration. B Medicine glass for 1 per cent novocain solution. C Bard Parker scalpel (no 11 blade) D 20 cc. Luer syringe E Aspirating needle (16 or 18 gage) with obturator in place F Semicircular scraper used to remove bits of tissue from barrel of syringe (glass slides.

material will be suddenly drawn and splashed over the interior of the syringe *making its collection difficult. While the needle is being advanced and with*drawn under negative pressure a small quantity of blood mixed with frag ments of tissue may enter the syringe, or a solid cylindrical mass of tissue may appear In other cases, especially in the firmer masses, the syringe apparently remains empty but after withdrawal, the needle is usually found to contain a plug of tissue.

After complete withdrawal of the apparatus the syringe is detached from the needle filled with air attached and the contents of the needle slowly and carefully expelled on a glass slide A small fragment of tissue should be left on the slide for smearing, and the remainder placed in the specimen bottle for

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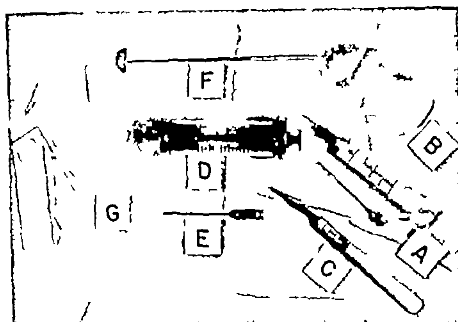


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After complete withdrawal of the apparatus, the syringe is detached from the needle, filled with air, attached, and the contents of the needle slowly and carefully expelled on a glass slide. A small fragment of tissue should be left on the slide for smearing, and the remainder placed in the specimen bottle for

fixation and staining by regular methods If the needle is empty small masses of tissue can almost always be found mixed with blood in the syringe, and these should, if necessary be very carefully searched for One or two of these small masses can readily be fished out upon a glass slide for smearing and immediate staining In any case where the syringe contains blood or any tissue formalin from the specimen bottle is poured into the open barrel of the syringe, agitated and returned to the specimen bottle

Preparation of the Specimen

There are two methods of preparing the specimen. The shorter requires about 20 minutes the longer about 2 hours If time permits the longer method has the advantages of providing a fixed, cleared preparation.

Short Method The fresh tissue fragment on the glass slide is smeared by very firm flat pressure by another glass slide drawn once across The smeared slide is fixed by heating gently over a gas flame until warm and dry and is then prepared according to the following technic

Step	Time
(1) Xylol	2 minutes
(2) 1st dioxane (or 95 per cent alcohol)	1 minute
(3) 2nd dioxane (or 95 per cent alcohol)	1 minute
( ) 95 per cent alcohol	1 minute
(5) 80 per cent alcohol	1 minute
(6) Water	1 minute
( ) Hematoxylin	1 to 2 minutes
(8) Thorough wash in water ammonia or lithium carbonate may be added if desired, followed by rinse in tap water	
(9) Eosin (aqueous or alcoholic)	1 to 2 minutes
(10) 80 per cent alcohol	1 minute
(11) 95 per cent alcohol	1 minute
(12) 1st dioxane	1 minute
(13) 2nd dioxane	1 minute
(14) 1st xylol	1 minute
(15) 2nd xylol	1 minute
(16) Mount in gum dammar or other suitable medium	

Longer Method The remainder of the specimen is handled like any other small biopsy specimen. It is embedded in paraffin pains being taken to collect every minute particle of the tissue

If it is essential to obtain a more rapid reading than can be had by the routine method, the following quick paraffin method of preparation which requires less than 3 hours may be used

(1) 10 per cent formalin	10 to 15 minutes
( ) 1st dioxane	10 minutes
(3) 2nd dioxane	10 minutes
(4) Equal amounts dioxane and paraffin	10 minutes
(5) 1st paraffin	15 minutes
(6) 2nd paraffin	30 minutes

(First 4 steps in oven at 3° C., last 2 steps in oven at about 56 C)
( ) Cut mount, and stain.

Present Concepts of Certain Tumors and Tumorlike Lesions of Bone

In recent years a number of neoplastic and non neoplastic lesion of the skeletal system have been described, and in some instances renamed, so that it seems best to enumerate them and to outline some of their distinguishing features

A Fibrocystic Lesions

Twenty five years ago the term osteiti fibrosa cystica wa used to include the so-called simple bone cyst the bone changes of hyper parathyroidism, and certain other entities especially fibrous dysplasia. These somewhat similar clinical entities are now rather generally differentiated. Bone cyst is a disease of childhood and adolescence and is usually seen in certain long bones e.g., the proximal portion of the humerus femur tibia and distal radius and ulna. The location of the process is rather constant and is in the juxtaepiphyseal (metaphyseal) area of the shaft. The cyst may have a distinct fibrous lining and contain clear straw-colored fluid or it may be partially filled with fibrous tissue Hyperparathyroidism (Recklinghausen s disease of bone) causes a diffuse polyostotic rarefaction of most or all of the skeleton (*see* Fig. 38) Not infrequently it is associated with calculi in the kidney and hypercalcemia and a mild increase in the serum alkaline phosphatase are constant findings

Fibrous dysplasia is a rather clearly defined condition which was independently described by Jaffe and co-workers and at about the same time by Albright and associates Jaffe at first used the term "polyostotic fibrous dysplasia" and Albright used the designation "osteitis fibrosa generalisata with pigmentation and sexual precocity in the female" Later Jaffe realized that the lesions were not always polyostotic and that not all of those that were presented the

other changes Albright had depicted Indeed Schlumberger found in material from the Army Institute of Pathology that by far the great est number of cases were monostotic and uncomplicated by sexual precocity or pigmentation

At present therefore we recognize three degrees of fibrous dysplasia (*1*) simple monostotic form (Fig. 3) (*2*) polyostotic form without other features (*3*) polyostotic form with cutaneous pigmentation and precocity of sex especially in females.

We believe the simple monostotic variety to be susceptible of cure by conservative surgery e.g. ablation of diseased area by curettage or resection. The intermediate form may or may not present indications for surgical interference depending upon the degree and location of the process The cases of true Albright syndrome" are not, insofar as we have been able to determine responsive to any form of therapy

That sarcoma may develop on an area of fibrous dysplasia was first shown by Stewart and Coley who in 1945 reported two cases in detail Others have been observed since but have not yet been recorded in the literature. One of our cases was of the fullblown Albright syndrome type, while the other belonged in the group of polyostotic fibrous dysplasia without other changes.

A review of the earlier material on fibrocystic diseases of bone reveals the existence of this situation, and also the fact that it was called by various names such as multiple fibrocystic disease or osteitis fibrosa cystica disseminata.

B Nonosteogenic Fibroma of Bone

This term applied by Jaffe in 1942 to a group of eccentrical., placed subcortical lytic areas in the long bones, has not attracted as much attention as might be expected in view of his notable past contributions to the general subject of bone lesions Schlumberger raises the question as to whether solitary xanthoma of bone nonosteogenic fibroma and monostotic fibrous dysplasia are not actually identical lesions.

At present, we incline to the position taken by Jaffe, and believe that the lesion he describes deserves a distinct position This is particularly true because the roentgenographic appearance of these lesions seems quite distinctive (Fig 4) At this point it is well to bear in mind that the histologic appearance of tissue removed from

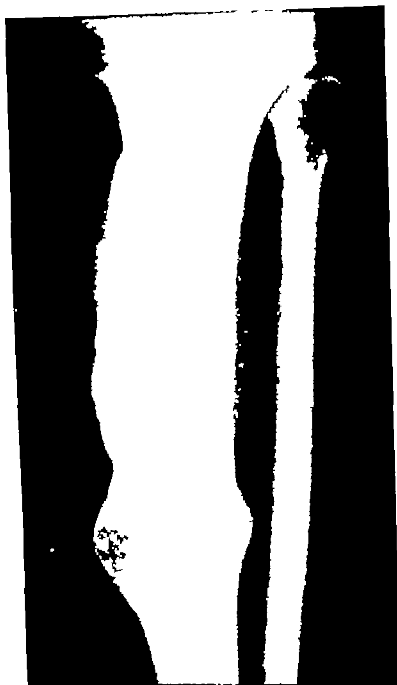


Fig 3. Fibrous dysplasia (monostotic form)



Fig 4. Nonosteogenic fibroma.

bone cyst from areas of hyperparathyroid alteration of bone or fibrous dysplasia and from nonosteogenic fibroma may be so similar as to make it impossible to decide from the microscopic picture alone which of these conditions is present in a given case

Thorough curettage of the affected area is all that is required to control the condition. The cavity, if extensive may be filled with bone chips.

C Osteoid Osteoma

This well-defined and now well recognized entity was also first described by Jaffe (49) He maintains that it i a specific bone neoplasm. Brailsford (4) Brown and Ghormley (5) and others on the other hand consider it to be an inflammatory lesion i.e., a subcortical abscess It gives rise to pain occasionally to slight swelling and localized tenderness and yields promptly to appropriate conservative surgery The roentgenographic features consist of a sclerosing area of bone, usually eccentric and poorly defined peripherally together with a small localized osteolytic area which is termed the nidus" (Fig. 5) Removal of this area en bloc is all that is necessary in the majority of instances to effect prompt complete and lasting relief of all symptoms

D Granulomatous Diseases of Bone of Uncertain Etiology

Included in a group of bone lesions believed to be of granulomatous nature and of obscure infectious origin are three allied conditions namely Letterer-Siwe disease Hand-Schüller Christian disease and eosinophilic granuloma. All three are believed to be related but it is not known with certainty whether they are different phases of the same disease process

Letterer-Siwe disease is confined to children under the age of 2 years and has a serious usually fatal outcome

Hand-Schüller-Christian disease occurs in children It is characterized by lytic lesions in the bones including the calvarium (maplike skull) at times it is associated with diabetes insipidus and exophthalmos. The response of the skeletal areas of involvement to mild doses of roentgen therapy is often dramatic (Fig. 6)

Eosinophilic granuloma may be seen in childhood adolescence, and early life, but is uncommon after the age of 25 Here the lesions



Fig. 5 Osteoid osteoma (10). The central radiolucent area representing the nidus is present but barely perceptible in the print.



Fig 6 Skull changes in Hand-Schüller-Christian syndrome. A Appearance before treatment. B Appearance after mild doses of roentgen therapy

are usually single purely osteolytic, and give rise to well-defined, sharply outlined areas of bone destruction which may resemble osteolytic malignant bone neoplasms (Fig 7) The histologic picture is quite characteristic and yet in the past it has been confused with other diseases especially myeloma of a type other than the plasma cell form

Curettage of the lesion is usually followed by healing and a lasting cure. Wounds should of course be sutured and never drained or packed Mild roentgenotherapy may also be employed often with satisfactory results.

These three conditions were at one time thought to be similar to Niemann Pick and Gaucher's diseases and consequently due to a disturbance of lipid metabolism Some writers still believe that they belong in this category

E Reticulum Cell Sarcoma of Bone

The existence of a specific primary malignant bone tumor composed of reticulum cells distinct from Ewing's sarcoma and not merely a manifestation of reticulum cell lymphosarcoma of lymph node origin was first demonstrated by Parker and Jackson in 1939 Their communication was based upon a series of 17 cases collected from several large Boston hospitals.

Some controversy has been aroused as to whether this condition is really distinct from Ewing's sarcoma Those pathologists who follow the line of reasoning put forward by Oberling (63 64) do not admit that the two diseases are separate entities but the majority feel that Parker and Jackson's arguments constitute a valid reason for believing that reticulum cell sarcoma is a definite neoplasm of bone (page 499)

Benign Tumors of Bone

The following are considered as benign bone tumors

Osteoma	Hemangioma
Osteochondroma	Benign giant cell tumor
Osteoid osteoma	Bone cyst
Central chondroma	*Fibrous dysplasia*
Benign chondroblastoma of bone	Nonosteogenic fibroma

By the designation *benign* one infers that the lesion does not metastasize nor recur after complete removal, and even if untreated



Fig 7 Eosinophilic granuloma. Solitary lesion in a 17 year old boy Curettage and chemical cauterization were followed by a satisfactory recovery

does not cause death. Yet in the case of benign bone growths, it is well recognized that they may ultimately have serious potentialities. Adamantinoma often grows in a period of several decades to a size which may indirectly cause the patient's death. Chondroma may undergo malignant transformation (Fig. 25) and the same is true of giant cell tumors and even fibrous dysplasia. The recognition of benign bone neoplasms and the decision as to whether they should be treated or left alone is therefore important.

Benign bone tumors grow at a slow rate or remain stationary, tend to expand rather than actually to destroy bone and infrequently cause pain although to a much slighter degree than do true sarcomas.

Roentgenographic examination is distinctly helpful in deciding whether or not a bone tumor is benign. The finding of a discrete and smooth outline of the tumor, an absence of irregular destruction or proliferation, and the expansion of a central lesion without a break in the cortex, all are indicative of a benign tumor. Nevertheless, it may be difficult or even impossible at times to decide on the basis of the roentgenograms alone whether a tumor is malignant or benign.

In some types of benign bone tumor, for instance osteochondroma, mechanical pressure of the lesion may affect the otherwise uninvolved paired bone, e.g. the ulna or fibula in cases affecting the radius or tibia. Since only slow growth and prolonged pressure will produce such distortion, the finding is strongly indicative of a *benign growth*.

Treatment

In the past there was little uniformity in the management of benign bone tumors; usually those which caused no symptoms were left alone. While one may be disinclined—and justifiably so—to subject a patient without symptoms to an extensive procedure for a benign tumor not readily accessible, there seems to be no valid objection to removing one from a region that is easily approached. In the case of central chondroma, particularly of the ribs and sternum, a prophylactic removal may protect the patient from a *malignant transformation which usually proves fatal*.

We are strongly opposed to the use of roentgen therapy for the majority of benign growths of bone. They are no more radiosensitive than normal bones, and dosages sufficient to inhibit their growth will

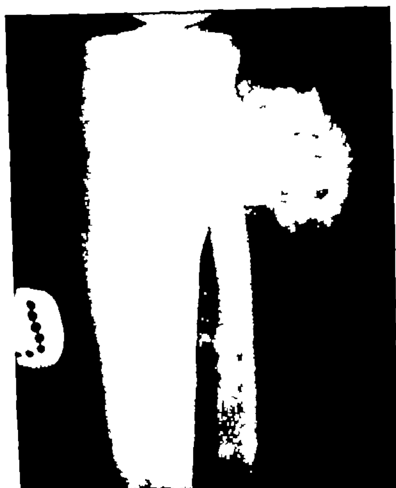


Fig 8. Osteochondroma of tibia. Such lesions require removal because they cause pressure on nerves and blood vessels.

necessarily have an adverse effect on contiguous uninvolved osseous tissue

Surgical Measures The following are measures which can be successfully employed in the treatment of benign tumors of bone (*1*) Excision (partial or total) (*2*) Curettage. (*3*) Resection (partial or total) (*4*) Segmental resection with bone transplantation. (*5*) Amputation.

Excision is applicable to osteochondroma exostosis and osteoma It should be wide enough to accomplish removal of the entire affected portion of the bone (Fig. 8)

Resection may be indicated in some cases of central chondroma or fibrous dysplasia Segmental resection, with replacement by massive bone transplant, has a useful place in the treatment of the essential long bones where any less radical procedure cannot be expected to lead to a permanent recovery (Figs. 10A–B and 11)

Amputation is rarely indicated for nonmalignant lesions, but occasionally it is required to save the patient from an almost certain late malignant transformation (see Fig. 22)

Treatment of Giant Cell Tumor by Irradiation It is apparent that there are still many authorities who maintain that giant cell tumor can be best managed by roentgen therapy Cutler Buschke and Cantril (24) have compared the surgical and radiotherapeutic methods and commented most unfavorably on the results of the former They hold the opinion that surgery entails impaired joint function and a recurrence rate of 25 to 30 per cent, whereas irradiation has a less unfavorable effect on joint function, results in at least as high a percentage of cures as surgery and accomplishes a permanent recovery in almost every instance in which an adequate dosage is used

We regard this statement as misleading and not supported by the experience of most of the authorities in the field of bone tumors. For example Geschickter believes "irradiation is far slower in its effects and disables the patient for too long a time he prefers surgery for those patients whose joint function is vital to their occupation and livelihood

Many years ago Bloodgood stated that the greatest danger from *irradiation is to persist in it too long* especially if the bone lesion is resectable.

In our experience at Memorial Hospital the end results of treatment by irradiation have *not been as satisfactory as those obtained* by conservative surgery Moreover a recent and as yet unpublished study of 11 cases of benign tumors of bone including bone cyst and giant cell tumor has indicated *an inherent danger in roentgen treatment* of such lesions in all of the 11 cases a late development of sarcoma occurred in the bone at the site of the irradiation (6a)

If one elects to treat a case of giant cell tumor by means of roentgen rays this should be the *sole* method employed no preoperative or postoperative radiation therapy should be used A few surgeons still give preoperative roentgenotherapy and some administer it

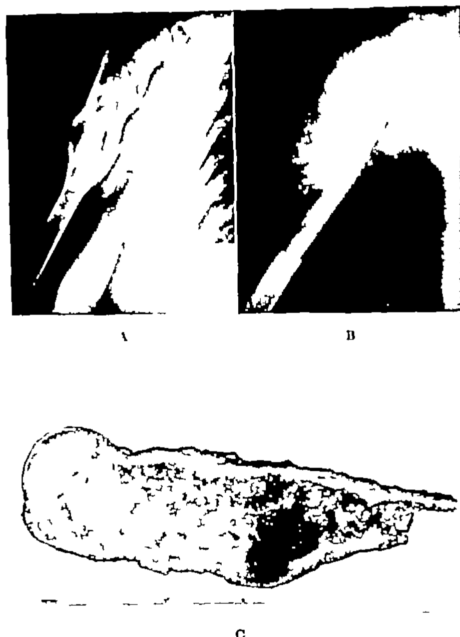


Fig. 11. Low grade chondrosarcoma of humerus. A. Appearance before operation, symptoms present for 2½ years. B. Postoperative roentgenogram. The upper two-thirds of the humerus was resected and replaced by the proximal fibula. C. Cross section of the gross specimen.

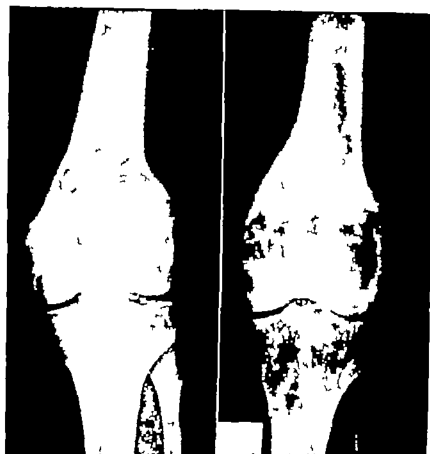


Fig 12 Giant cell tumor A Original roentgenogram B Result 11 years after roentgen therapy good functional result

after operation, but the majority prefer not to combine surgery and irradiation Our dictum is "The treatment of giant cell tumor is either irradiation *or* surgery" (Fig 12)

Selection of Cases for Roentgen Therapy In general it is believed that surgery is preferable to roentgen therapy for the accessible lesion in a long bone for inaccessible lesions e g neck of femur sacrum or spine radiation methods are indicated Using 125–150 kv and a 4 mm. Al filter at a target-skin distance of 30 cm. each portal

(usually 2) is given 500 r units at a single dose this is repeated after an interval of 4 to 7 days Thus a cycle consists of 4 treatments 2 to each portal If one uses a higher voltage (200 to 250 kv) the factors are modified by lowering the dose per treatment and by increasing the number of treatment The size of the portals must of course be taken into consideration and the dose should be calculated in terms of what is actually delivered to the most deeply situated portion of the tumor (tumor dose or depth dose)

Following the administration of a course of therapy there is a period when subjective symptoms and objective signs become more marked The patient is aware of increased discomfort, and the tumor-bearing area tends to swell Such immediate sequelae are not to be interpreted as indicating increased growth activity and should not be regarded as the signal for another series of treatments Such an interpretation has in the past resulted in dosages exceeding those we now realize to be a safe maximum and production of damage to skin soft tissues and bone with ultimate loss of the limb Fortunately since roentgenologists have become aware of the hazards of excessive irradiation such untoward complications are now infrequent.

Whether the method employed is curettage or roentgenotherapy the limb should be supported during the period required for bone regeneration lest a pathologic fracture occur This is particularly true of cases involving the bones of the lower extremity because of the almost certain impairment of function which follows

When symptoms progress after treatment and there is roentgenographic evidence of continued bone destruction the temptation to administer more roentgenotherapy is strong When this is done and the symptoms and signs indicate that healing of the lesion is still not progressing there is a possibility that one is dealing with a malignant tumor or with a benign giant cell tumor that is undergoing malignant alteration An aspiration biopsy may be performed and this may decide the issue Despite the hazards inherent in surgical biopsy following heavy irradiation such a procedure may at times be required to reach the correct diagnosis

No more troublesome problem arises in the field of bone neoplasms than that posed by a giant cell tumor which fails to yield to adequate

well planned doses of roentgen therapy Granting that such a situation is uncommon it does nevertheless occur frequently enough to influence us in favor of surgical treatment from the outset for accessibly located benign giant cell tumors

Malignant Tumors

OSTEOGENIC SARCOMA

This designation has been widely accepted as the generic term for those primary malignant tumors which are derived from bone. This group includes varieties which in the past were called periosteal sarcoma osteosarcoma, central or medullary sarcoma or polyhedral cell sarcoma.

Ewing (29) in 1939 revised the earlier *classification of the Bone Sarcoma Registry* of the American College of Surgeons, and listed the subdivision of osteogenic sarcoma as follows

(a) Medullary and subperiosteal	(d) Periosteal
(b) Telangiectatic	(e) Fibrosarcoma (medullary and periosteal)
(c) Sclerosing	(f) Parosteal capsular

For the first time Ewing placed sarcoma of cartilaginous origin in a separate category instead of including it among the varieties of osteogenic sarcoma

There are reasons—which to us seem valid—for removing from the osteogenic group both the medullary and the periosteal fibrosarcomas as well as the parosteal and capsular types In our opinion these may be justifiably considered as derived from cells destined to form supporting (connective) tissues, and no indication is offered that they arise from cells of the bone-forming series Of particular importance is the fact that these fibrosarcomas have a much more favorable prognosis than that of the other types of osteogenic sarcoma. They grow more slowly metastasize less early and the percentage of 5-year survivals is markedly higher For the reasons just mentioned it has seemed to us and to other workers that fibrosarcoma of bone deserves a separate grouping and should not be placed among the osteogenic sarcomas. Capsular and parosteal sarcomas that do not form bone may also be regarded as fibrosarcomas provided of course that one excludes those of true synovial origin—the malignant synoviomas, and those spindle cell

TABLE V

Age Incidence of Osteogenic Sarcoma Among 160 Patients

Age years	Number of cases	Number dead of disease	5-yrs. survival number	5 yrs. survival per cent
1–10	8	[illegible]	1	12.5
11–20	57	45	12	21.1
21–30	25	1[illegible]	8	32.0
31–40	26	18	8	30.8
41–50	19	17	2	10.5
51–60	13	12	1	[illegible].7
61–70	11	8	3	27.3
71–75	1	1	0	—
Total	*160*	*[illegible]*	*35*	*21.9*

TABLE VI

Bone Involved in 257 Consecutive Cases of Osteogenic Sarcoma Treated at Memorial Hospital from 1917 to 1940 Inclusive

Bone	Number of cases
Femur	120
Humerus	43
Tibia	33
Ilium	22
Rib	11
Fibula	13
Scapula	11
Radius	6
Os Calcis	4
Metatarsal	4
Sternum	3
Ischium	3
Sacrum	3
Clavicle	2
Pubis	2
Lumbar vertebra	2
Ulna	1
Phalanx	1
Total	257

tumors of muscle or nerve origin which may at times involve bone by direct extension

In the United States osteogenic sarcoma affects one in every 100,000 persons while in England it is estimated that one in every

75 000 is afflicted. Males are more often subject to the disease than females, in the proportion of 60 to 40 It may occur at any age although it is essentially a disease of adolescence and young adult life The age incidence in a series of 160 osteogenic sarcomas observed at Memorial Hospital is shown in Table V

The bones most often involved are femur humerus tibia, and ilium The femur accounts for almost 40 per cent of all cases as may be seen in Table VI

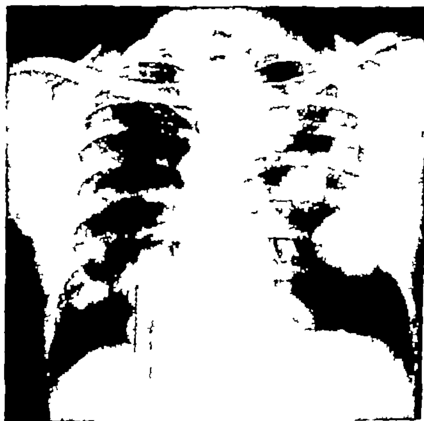


Fig 13 Pulmonary metastases from osteogenic sarcoma

Clinical Features Pain is the predominant early symptom it is insidious in its onset transitory at first but later becomes constant and more severe until it is of a boring, excruciating nature requiring sedation for its control

Tumefaction often absent at first, gradually becomes apparent, and is diffuse, ill-defined and often eccentric Its consistence is

variable but it is always firm and sometimes is stony hard; sometimes elastic or rubbery. The skin gradually changes in appearance and there is increased warmth of the affected area and often dilated superficial veins due to tumor thrombi in the deep veins (Fig. 1).

Disability may vary considerably in the early stages but ultimately it is always pronounced. In the majority of cases the limbs are the site of the disease. When the lower extremity is affected a limp is noticed and failure of complete flexion or extension is complained of or is observed by the examiner. Despite these symptoms the adjacent joint is seldom invaded.

Discomfort in the chest with or without cough is a symptom of pulmonary metastasis (Fig. 13). Hemoptysis is unusual until late in the disease. Because the lungs may already be affected when the patient is first seen it is imperative that anteroposterior and lateral films of the chest be made a part of the initial examination. The case should be studied and worked up according to the plan outlined in Table II.

Blood Chemistry Studies. As in every suspected bone neoplasm one should examine the blood for calcium, alkaline phosphatase and inorganic phosphorus (see section on "Blood Chemistry in Bone Neoplasms").

TABLE VII

Clinical Value of Determination of Alkaline Phosphatase in the Serum in Diagnosis and Prognosis of Osteogenic Sarcoma

Alkaline phosphatase in serum	On admission	High	Osteoblastic lesion: confirms diagnosis of osteogenic sarcoma
			Osteolytic lesion: prognosis very poor; tumor growing rapidly
		Slightly elevated	Osteoblastic lesion: prognosis good; tumor growing slowly
			Osteolytic lesion: confirms diagnosis of osteogenic sarcoma
	After treatment		Fall to normal: prognosis good
			Failure to fall to normal: prognosis poor; still viable tumor in primary or metastatic areas

Resection, amputation, or radiation therapy

Value of Phosphatase Determination. One gains information from the phosphatase level in the serum that is of value in estimating the activity of an osteogenic sarcoma as may be seen from the summary given in Table VII.

Roentgenographic Examination. The roentgenographic appearances are usually rather striking and vary according to the type of



Fig 14 Osteogenic sarcoma in a 34 year old woman with metaphyseal involvement in the form of a globular tumor in contrast to the ordinary fusiform shape Patient is alive and well, 22 years after shoulder joint disarticulation.



Fig 15 Periosteal form of osteogenic sarcoma (chondrosarcoma type) The roentgenographic features are those of a periosteal osteogenic sarcoma but microscopic examination revealed chondromyxosarcoma.

osteogenic sarcoma present (Figs 14 and 15) In general the *roentgenogram reveals a destructive lesion which may be purely* osteolytic or accompanied by varying degrees of osteoblastic reaction (Fig. 16) If the cambium layer of the periosteum is involved primarily or by invasion dense tumor bone is laid down giving a predominantly osteoblastic appearance. In many instances the periosteum at the margin of the tumor deflects sharply from the normal bone creating the so-called Codman's triangle which is practically pathognomonic for osteogenic sarco rule, the lesion

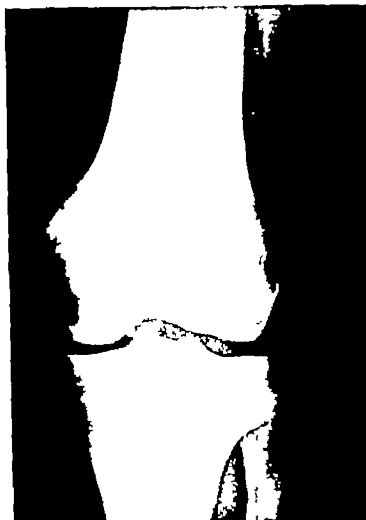


Fig 16 Osteogenic sarcoma, medullary spindle cell type. This is an early lesion, symptoms having been noted for only 6 weeks

tends to be pear-shaped is irregular in shape and outline and lacks clearly defined margins between it and the normal bone (Fig. 17) In rapidly growing or telangiectatic varieties, the entire outline of the bone may be lost and pathologic fractures are common.

Differential Diagnosis

In a case suspected of being osteogenic sarcoma or chondrosarcoma one must consider four other possibilities namely (*1*) some

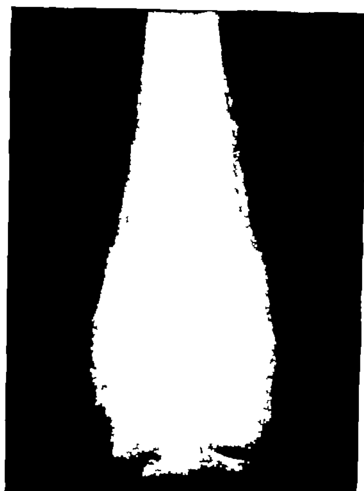


Fig 17 Osteogenic sarcoma The appearance is classic for example (*1*) position in the metaphysis, (*2*) pear-shaped swelling, (*3*) well-marked Codman's triangle, (*4*) striations perpendicular to the shaft.

other type of primary bone sarcoma, (*2*) metastatic cancer in bone, (*3*) a benign bone neoplasm and (*4*) a non neoplastic bone affection.

It is important to rule out these four possibilities for the treatment in all four differs from the appropriate one for osteogenic sarcoma. For example one might well elect to treat Ewing's sarcoma or reticulum cell sarcoma by roentgenotherapy one would probably not amputate for metastatic cancer in bone one would surely hope to avoid radical surgery such as amputation for benign bone neo-

plasms and finally the therapy for the large miscellaneous group of non neoplastic diseases of the skeletal system differs from that for bone sarcoma and individually within the group

Other Types of Primary Bone Sarcoma *Endothelioma* This tumor frequently originates in the metaphyseal region of a long bone and produces the triad of pain swelling and disturbed function It does not produce tumor bone radiating trabeculae at right angles to the shaft are not seen yet it is often associated with reactive bone The lamellar appearance parallel to the long axis and the tendency to involve a greater extent of the shaft are features that should help to distinguish it from osteogenic sarcoma Of great importance is the age of the patient endothelioma is rarely found in persons past the age of 30 while osteogenic sarcoma may occur at any age In many instances these conditions cannot be distinguished with certainty except by a microscopic study of the section

Reticulum Cell Sarcoma This rare tumor bears a much closer resemblance to endothelioma both roentgenographically and microscopically However like endothelioma, there are instances in which it may closely simulate osteogenic sarcoma and histologic proof is the deciding factor Like endothelioma this tumor too is radiosensitive and the character of its response to therapeutic roentgen irradiation may prove strong corroborative evidence

Metastatic Cancer in Bone This condition can simulate osteogenic sarcoma, especially when only one area is demonstrable however as middle adult life is reached the latter disease becomes less common. On the basis of probabilities the likelihood of a suspected osteolytic lesion being metastatic rather than primary in a person over 40 years of age is better than two to one In patients over 30 a complete skeletal roentgenographic examination is indicated if more than one area of bone is involved there is the strongest likelihood that the origin is from a carcinoma A careful search for a primary source elsewhere is uniformly indicated but if none is found it cannot be assumed that the lesion is a sarcoma.

Benign Bone Neoplasm. Giant cell tumor only infrequently resembles osteogenic sarcoma Confusion may arise when one attempts to determine whether a central area of bone destruction in the epiphyseal region is due to an osteolytic medullary fibrosarcoma, to a central nonbone-forming osteogenic sarcoma or to an aggressive giant cell tumor Malignant giant cell sarcoma, although rare may

afford a most difficult problem in view of its resemblance to osteolytic osteogenic sarcoma.

Non-neoplastic Bone Disease. Non neoplastic conditions may bear only a slight resemblance to osteogenic sarcoma or may be difficult to differentiate. The various conditions to be taken into consideration are shown in Table VIII

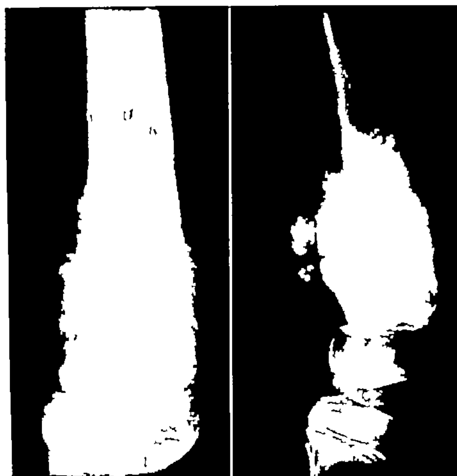
TABLE VIII

Non-neoplastic Conditions of Bone That May Resemble Neoplasms of Bone

Non-neoplastic conditions	Neoplasms
Infections	
Pyogenic	Endothelioma
Typhoid	Myeloma
Syphilis	Almost any form of bone tumor
Tuberculosis	Myeloma of spine synovioma with bone involvement
Chronic sclerosing osteitis	Sclerosing osteogenic sarcoma
Parasitic diseases	
Hydatid	Osteogenic sarcoma
Fibrocystic diseases	
Solitary bone cyst (unicameral)	Giant cell tumor central chondroma
Hyperparathyroidism	Skeletal metastases from carcinoma
Fibrous dysplasia	Central chondroma, nonosteogenic fibroma
Diseases of uncertain etiology	
Osteitis deformans	Monostotic form (osteogenic sarcoma) polyostotic form (metastatic prostatic carcinoma)
Leontiasis ossium	Low grade sarcoma
Osteoid osteoma	Sclerosing osteogenic sarcoma
Lipid storage diseases	
Hand-Schuller-Christian disease	Metastatic carcinoma
Eosinophilic granuloma	Primary osteolytic osteogenic sarcoma
Circulatory disturbances of bone	
Aseptic necrosis of bone	Chondroblastoma
Calcinosis (tumoral form)	Sclerosing osteogenic sarcoma
Disturbances due to injury	
Ossifying hematoma (myositis ossificans)	Osteogenic sarcoma
Fatigue fracture (early reparative stage)	Osteogenic sarcoma, or endothelioma
Periosteal injuries (early stage)	Osteogenic sarcoma (early)

Radiation Therapy

Our early expectations that radiation therapy of osteogenic sarcoma might prove successful and thus render mutilating surgical measures unnecessary have unfortunately not been realized At present we feel that the only indications for roentgen therapy in this disease are (*1*) For totally inoperable cases. (*2*) For the excep-



A B

Fig. 18. Osteogenic sarcoma (42) A Before treatment. B After preamputation roentgen therapy (9,000 r units tissue dose)

tional case in which permission for amputation has been persistently refused. (3) For any case in which a delay in obtaining permission to amputate is anticipated. (4) For those rare anaplastic and radiosensitive cases occurring in infants or very young children in which the prognosis after amputation alone is nearly hopeless (Fig. 18) (5) For palliative purposes in the presence of established pulmonary metastases

A study of the effects of irradiation on osteogenic sarcoma by Woodard and Coley (81) disclosed that in the adult a single course

of treatment of 3 000 r or less given in a period of several weeks was not followed by a permanent loss of bone regenerative powers, while doses of 3,000 to 4,000 r usually gave rise to some evidence of permanent damage to bone It is apparent that with doses above 5 000 r there is a permanent and complete loss of the regenerative capacity of bone even when the total dosage is arrived at over a considerable period of time (several courses)

In young subjects, on the other hand it was observed that although doses as small as 600 to 1,500 r may cause a temporary reduction in the rate of epiphyseal growth and larger doses may cause complete cessation of growth nevertheless the regenerative capacity exceeds that of adult bone and it resists radiation injury better Four of our cases tolerated doses in excess of 5,000 r without severe damage (Fig 18)

We conclude that doses up to 4 000 r may be used in the adult with the probability that permanent damage to bone will not preclude the retention of a considerable degree of useful function With doses larger than 4 000 r it may be anticipated that ultimate results will be unsatisfactory or even disastrous

Our experience with 39 cases of osteogenic sarcoma treated by irradiation has led us to the following conclusion Tumor doses of less than 4,000 r produce only irregular and transitory control of the disease doses from 4 000 to 8,000 r may induce control for a number of months, but it requires approximately 8 000 r to effect a permanent devitalization of osteogenic sarcoma. Since such dosage is far in excess of the tolerance of the adjacent normal bone radiation therapy obviously does not afford much hope of a permanent control of this disease however it may be a useful palliative agent in patients who either refuse surgery or in whom the disease is inoperable

Technic It is desirable to use multiple portals depending on the size, shape and position of the primary tumor 2 is the usual number, but 3 or more are feasible under certain conditions. The exit dose must be allowed for when portals opposite each other are employed

Voltage of 200 to 250 kilovolts has accomplished as much as the 1,000,000 volt therapy in the average case Doses of 200 to 250 r units are given daily and the various portals are treated in rotation. A total dosage of 2,500 to 3,000 r can be delivered to each portal without excessive skin damage (42)

The record should include an estimate of the actual depth dose or "tissue dose." A discussion of the effects of the various factors on tissue dose" may be found in the treatise by Glasser, Quimby, Taylor and Weatherwax (38). By using the tables in the appendix of that book it is possible to calculate the tissue doses under most of the conditions encountered in the treatment of bone sarcoma.

Surgical Treatment

Resection. It would indeed be fortunate if the portion of the bone affected by osteogenic sarcoma could be resected without risk of regional recurrence and with preservation of a useful member. This however is seldom possible; with few exceptions most surgeons consider an immediate amputation indicated in osteogenic sarcoma of an extremity bone.

Under certain favorable circumstances, however, resection is a justifiable procedure. Phemister (68), as well as others, have cited excellent results with long term survivals with useful limbs. Figure 19 illustrates a case of ours.

Curettage of a central bone sarcoma is generally not to be recommended as a definitive measure. In extremely low grade tumors, e.g., some chondromyxosarcomas and fibrosarcomas, it may be justified in exceptional instances. Figure 20 serves to illustrate the successful employment of curettage in such cases.

It should be emphasized that judgment is required in the selection of cases in which either resection or curettage is attempted. These measures find their chief justification in the occasional case where, though amputation is strongly urged, it is nevertheless refused.

Amputation. This drastic procedure is still the most reliable method of dealing with osteogenic sarcoma of the bones of the extremities. It is the method of choice for the vast majority of such cases. It is justified even in the presence of pulmonary metastases where it serves a useful purpose as a palliative measure.

Level of Amputation. For years it has been the accepted practice to amputate proximal to the affected bone—never through it. While from a practical standpoint it makes little difference to the patient whether he has a shoulder joint disarticulation or an interscapulothoracic amputation, it is of great importance whether he has a high thigh amputation or a hip joint disarticulation. Moreover, the lower end of the femur is the most frequent site for osteogenic sarcoma.



Fig. 19 Chondrosarcoma developing on an osteochondroma (9b) A–B Before operation C After resection of tumor saucerization, and chemical cauterization of the base P tient has been free of recurrence for 10 years.



Fig. 20. A Low grade medullary chondromyxo-sarcoma note similarity to giant cell tumor B Appearance 6 years after treatment by curettage and inlying bone graft from adjacent normal shaft of tibia.

We have maintained that for cases affecting the distal end of the femur one may in the majority of instances avoid a hip joint disarticulation by performing a high thigh amputation and thereby vastly increasing the patient's chances of being able to use an artificial limb satisfactorily. In a consecutive series of 39 amputations through the upper femur for osteogenic sarcoma of the lower third we found only 2 in which there was subsequent recurrence in the stump. One of these was then subjected to a hip joint disarticulation and is alive and well more than 10 years later. Thus it would appear that little additional assurance of a permanent recovery would have been gained had all of these cases had a hip joint disarticulation; certainly the 14 patients who passed the 5 year survival period had a much better chance to pursue a happier and more useful life because of the improved function made possible by an artificial limb. We know of some patients who have had a hip joint disarticulation and who can wear a prosthesis with fair satisfaction. In our experience, however, these are the exceptions; the majority prefer to use crutches.

Despite our belief that osteogenic sarcoma of the lower femur may usually be safely dealt with by high thigh amputation, we have generally followed the conventional concept in the case of other long bone sarcomas. Our reason has been that in most of these cases the difference to the patient is less important. Furthermore, the incidence of osteogenic sarcoma in the ankle or elbow region is low so that decision is not often required. However, we venture to suggest that the same principles as have been mentioned relative to the distal end of the femur also apply to other situations and we believe that a more conservative procedure may be adopted if care is exercised in selecting the individual case.

Figure 21A–C illustrates the proposed levels of amputation.

Interinnomino-abdominal Amputation. While this operation *has been performed for more than half a century (2)* the shocking mortality of over 50 per cent during the first 40 years of this period did not encourage its use nor add to its popularity. To Gordon Taylor (39) belongs the credit for reviving interest in it. In 1935 he reported 5 cases and gave a description of his technic. He added 6 more cases in 1940 in which the operative mortality was 33 per cent.

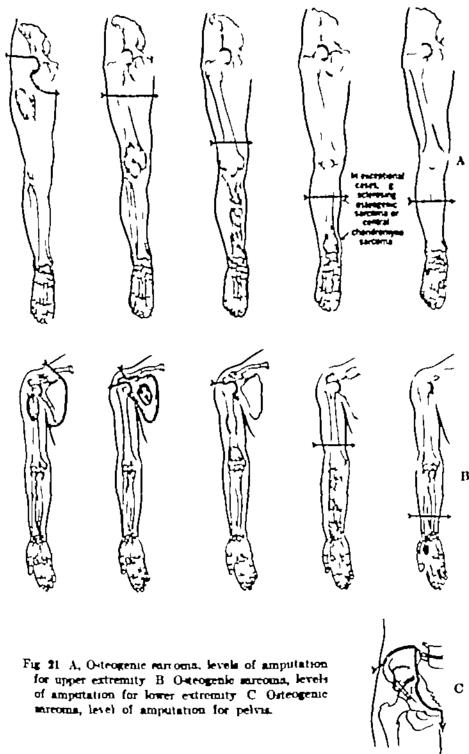


Fig 21 A, Osteogenic sarcoma, levels of amputation for upper extremity B Osteogenic sarcoma, levels of amputation for lower extremity C Osteogenic sarcoma, level of amputation for pelvis.

Sugarbaker and Ackerman (80) in 1945 collected 126 cases from the literature and added 6 more of their own in which the mortality was also 33 per cent. In 1946 Pack and Ehrlich (65) reported 6 cases from Memorial Hospital in which there was not a single operative fatality We have done 6 without a death.

Sugarbaker and Ackerman found that the mortality rate for all reported cases up to 1945 was 28 per cent but that it had fallen from 56 per cent in the first 40 years to 14 per cent in the past 10



Fig 22A Enormous osteochondroma of ilium

years Unquestionably the reason for this marked improvement lies in better preoperative preparation, unlimited use of blood trans fusions and more skillful anesthesia and thus a reduction of surgical shock which is the principal hazard

Bone tumors of the innominate bone and upper femur are prom inent among the conditions for which this operation may be indicated (Fig. 22A–D)

Preoperative Measures Correction of anemia by blood transfusions is imperative Repeated at intervals of 2 or 3 days, in most cases it is possible to bring the hemoglobin up to normal levels. A careful skin preparation, including the external genitalia, is essential. A self retaining catheter of the Foley type is inserted before the patient arrives in the operating room.

Anesthesia Since it is highly desirable that the patient be asleep either nitrous oxide-ether or cyclopropane anesthesia is satisfactory We do not recommend continuous spinal anesthesia combined with



Fig. 22B Roentgenogram of the tumor Stereoscopic study revealed projection of the tumor into the pelvis as well as posteriorly

intravenous administration of sodium pentothal because of the depressing effect of the former upon the blood pressure

Operative Technic A sandbag placed beneath the sacrum tilts the pelvis toward the unaffected side thus permitting much of the operation to be performed without changing the patient's position. In the male a towel clamp is used to secure the scrotum to the opposite thigh this keeps the genitalia out of the operative field.

Following the directions given by Pringle in 1916, the incision



Fig 22C Appearance 4 months after hemipelvectomy Sections from various portions of the tumor revealed osteochondroma. This type of tumor is prone to undergo chondrosarcomatous change

begins at the anterior-superior spine and extends to the pubic symphysis along Poupart's ligament. Posteriorly it runs along the crest of the ilium crosses above the greater trochanter and extends along the gluteal crease to the perineum Here it turns forward to join the



Fig. 22D Another patient wearing artificial limb 3 months after hemipelvectomy This patient a musician stood for 3 hours on stage 10 days after being fitted with his prosthesis.

medial end of the anterior incision immediately above the pubic symphysis

The inguinal ligament is divided at its lateral and medial attach

ments and the anterior abdominal wall is raised as the anterior flap. The spermatic cord is reflected medially and held out of the way by a tape The peritoneum is carefully stripped upward and medially along with the abdominal contents and held in this position by large laparotomy pads The bladder is displaced medially and inferiorly which exposes the iliac fossa. The ureter should always be identified at this point and together with the rectum and bladder should be kept out of the operator's way

The bifurcation of the iliac artery is now readily recognized and after the operator has decided that the case is operable the external iliac artery is ligated The internal iliac artery is temporarily occluded by means of a special rubber-covered clamp (seraphin) The external iliac vein is then ligated after the limb is elevated for one or two minutes

The pubic symphysis is now denuded of all its soft part coverings, *including the insertion of the rectus abdominis, and divided with a* Gigli saw or a chisel (we prefer the latter) Some writers warn of troublesome hemorrhage during this step but we have not encountered it. Packing and pressure temporarily applied or the use of fibrin foam or oxidized gauze left in place should control bleeding satisfactorily

The crest of the ilium is now skeletonized by dividing the muscles which attach to it. The iliopsoas, iliacus, piriformis, gemelli and levator ani muscles are all severed as high as possible, exposing the sacroiliac joint. This is disarticulated using a broad chisel or osteotome. One should as Pack and Ehrlich (65) advise, direct the chisel away from the midline and carefully avoid injuring the hypogastric vein. Packing may here be required to control bleeding. The gluteal muscles are now divided, and the major ligaments of the sacrum also are cut. All that remains are the major nerve trunks including the sciatic After division and ligation these are injected with novocaine and then with alcohol The specimen is now free and is removed.

Closure resolves itself into approximation of an anterior and a posterior flap using interrupted sutures and exercising meticulous skin approximation. Rubber dam drains or Penrose drains are made to emerge at the angles of the wound and a bulky voluminous gauze dressing is fastened with evenly distributed moderately firm pressure Elastoplast is useful to retain this dressing in place

Blood transfusion sets are ready during the early stages of the operation and use of the contralateral arm and foot permit simultaneous inflow of blood at a rapid rate during the critical periods of the operation e g., when the sacroiliac joint is divided Large amounts of blood are required and should be at hand Recently we used 2 liters of whole blood and 1 liter of plasma during the 3 hours required to perform the operation This enabled us to return the patient from the operating room with a blood pressure a trifle higher than it was when the anesthesia was begun.

Postoperative Care When the patient regains consciousness a Levin tube may be passed and Wangensteen suction instituted or one may wait until signs of early distention appear In any case its use is seldom required after the first 48 hours when gas is usually passed and a soft diet is tolerated Tidal drainage is connected to the urethral catheter and prevents overdistention of the bladder until its tone is restored and normal urination takes place

Further supportive measures such as blood and plasma transfusions are often required and are given as indicated by frequent checks on the electrolyte plasma protein and hematocrit levels Infusions also contain large doses of vitamins

Those who favor early ambulation as we do will find it possible to get these patients up on the second or third postoperative day

Chemotherapy is indicated because it is impossible to avoid some contamination of a wound that is large and vulnerable to infection Penicillin in doses of 50,000 units every 3 hours is given prior to operation and continued for a week or 10 days or until the danger of infection is passed. Streptomycin can be used to combat organisms of the Escherichia coli group contamination with which is favored by the location of the perineal portion of the incision.

Drains ought not to be removed as early as is deemed advisable in other types of amputation because drainage may be profuse for many days and must be allowed to escape

Results. Although osteogenic sarcoma (including chondrosarcoma) is generally regarded as a hopeless disease, a critical analysis of the Memorial Hospital series reveals the encouraging 5 year survival rate of 21 9 per cent in a determinate group of 265 consecutive cases from 1917 to 1940 as shown by Table IX. The results in another group according to age are given in Table V on page 451

TABLE IX

Memorial Hospital Series of Osteogenic Sarcoma (Including Chondrosarcoma) from 19[illegible] to 1940 Inclusive

Description	Number of cases
Clinical diagnosis	3[illegible]
Without histologic verification	60
With histologic verification	273
Indeterminate group	8
Dead of other cause in less than 5 years without recurrence	6
Lost to follow-up without recurrence	2
Determinate group	265
Failures	207
Dead of sarcoma	193
Lost to follow-up with disease	11
Died of other cause but with disease	1
Postoperative deaths	2
Successes	
Free of disease 5 or more years after treatment	58
5 year survival rate (determinate group)	21.9%

TABLE X

Methods of Treatment in 58 Cases of Osteogenic Sarcoma (Including Chondrosarcoma) That Lived 5 or More Years*

Method	Number of cases	Totals
Amputation		52
Alone	12	
With preoperative radiation	10	
With postoperative toxins	10	
With toxins and radiation	20	
Resection or excision		4
Alone	2	
With preoperative radiation	1	
With radiation† and toxins	1	
Radiation without surgery		2
Alone†	1	
With toxins	1	
Total		58

* Five patients in this series died of sarcoma after 5 years.
† Radium needles.

The methods of treatment employed in the patients who survived 5 or more years are listed in Table X.

CHONDROSARCOMA

The term chondrosarcoma is applied to any malignant tumor derived from cartilage cells. While in the original classification

adopted by the Bone Sarcoma Registry of the American College of Surgeons this tumor was designated as a subgroup of osteogenic sarcoma Ewing in his revision placed all the tumors arising from or producing cartilage in a separate category Prior thereto their distinguishing characteristics had been emphasized by Phemister (67) and by others Morton (59) has recently reported a considerable group comprising his own cases as well as those of the Registry

It seems appropriate to subdivide chondrosarcoma into the two groups of primary chondroblastic sarcoma and secondary chondromyxosarcoma.

Primary Chondroblastic Sarcoma

This neoplasm is usually found in children and young adults The sites commonly affected are the distal portion of the femur and the proximal portion of the tibia and humerus (Fig. 23) It has its origin from cartilage in or near the epiphyseal area. The symptoms are not distinguishable from those which are caused by osteogenic sarcoma they include pain swelling and interference with function of the affected part Increase of the serum phosphatase may be present and its level is roughly proportional to the activity of the tumor Heavy radiation therapy may markedly reduce this level and amputation causes a fall to normal limits unless metastasis has occurred.

Roentgenographic examination reveals a relatively circumscribed area of increased density within which are seen areas of calcification Soon the cortical and cancellous bone is destroyed the periosteum is raised and there may appear reactive bone at the advancing margins of the tumor This is what gives rise to the term "Codman's triangle" This tumor has no features which enable one to make a positive roentgenographic distinction from osteogenic sarcoma (see Fig. 24)

The microscopic appearance is quite variable The sections may disclose cartilage and precartilaginous tissue or in the case of the more malignant highly anaplastic tumors almost completely undifferentiated tissue In such instances it may be impossible to distinguish them from those *osteolytic forms of osteogenic sarcoma* which are also highly undifferentiated. However this is a point of little clinical significance

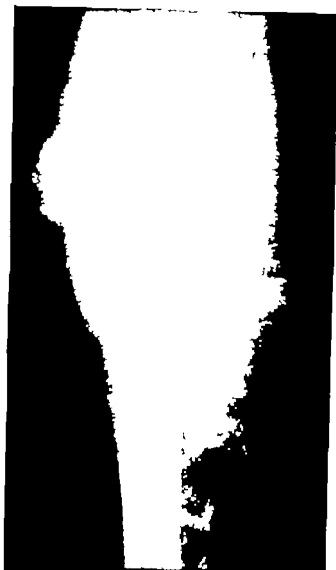


Fig. 23. Chondromyxosarcoma in an unusual location.

Secondary Chondrosarcoma

This form of chondrosarcoma is nearly always seen in adults and is due to a malignant alteration in the cells of a central chondroma (Fig. 25) an osteochondroma, or rarely on the basis of a multiple skeletal defect, such as hereditary deforming dyschondroplasia. It

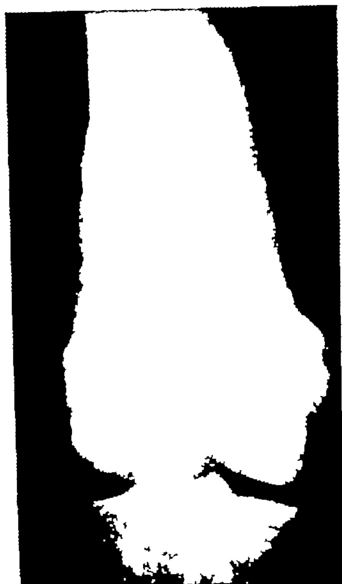


Fig 21 Typical chondrosarcoma. Roentgenographic appearance resembles that of osteogenic sarcoma, but microscopic examination revealed that it was chondrosarcoma.

occurs in a wide variety of locations, and has a greater tendency than the primary chondroblastic form to affect the scapula, ribs pelvis, and bones of the tarsus and metatarsus Of course, the long bones of the extremities are also frequently involved

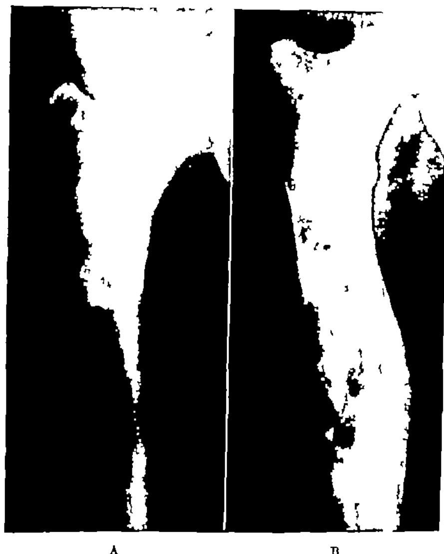


FIG. 25 A Central chondroma in a 64 year old woman the diagnosis was confirmed by biopsy B Transformation to chondrosarcoma 14 months later the diagnosis was established after hip joint disarticulation.

It may be difficult or impossible to determine conclusively the previous existence of a benign chondroma When however sarcoma is engrafted on a cartilaginous exostosis, the connection may be apparent and partial destruction of its contour together with additional new bone formation may be visible on roentgenographic



Fig. 26 Ollier's disease of the right lower extremity with malignant degeneration of the upper femoral portion, in an 11 year old boy (19). Patient died 2 years later from pulmonary metastases.

examination. In rare instances, sarcoma may develop in one of a number of cartilaginous defects such as is seen in hereditary deforming dyschondroplasia (Fig 26)

Secondary chondrosarcoma is one of the commoner forms of malignant tumors having their origin in the skeletal system in patients past the age of 35 Many of the cases collected by Morton fall into this group He found that in his 74 cases the average age was 38 Men are more often affected than women

In many cases there is unquestionable difficulty in distinguishing between central chondromyxosarcoma and benign central chondroma We have seen a substantial number of cases in which it was impossible to be certain on clinical and roentgenographic evidence whether malignant changes had occurred For this reason we consider it advisable to urge surgical treatment of central chondromas whenever they are found in accessible locations

Other lesions which may require differentiation are giant cell tumors and areas of monostotic fibrous dysplasia. Recently we saw a case of central chondromyxosarcoma of the proximal end of the tibia which had received roentgen therapy for about a year on the assumption that it was a benign giant cell tumor (Fig. 27A–B) Such mistakes have not been rare and they offer additional arguments for surgical treatment as opposed to irradiation, for benign tumors which lack histologic confirmation. Secondary chondrosarcomas vary markedly in their rate of growth and in the rapidity with which they metastasize It is not surprising therefore that their histologic appearance is also quite variable This is not only true as regards individual tumors but obtains in different portions of the same tumor One often finds histologically benign areas adjacent to others which are obviously malignant Generally the anaplastic areas are found at the periphery There is often much fibrous and myxomatous material interspersed with cartilage and there may be irregular calcification which is prominent in the roentgenograms. The central portion of the tumor may be necrotic, calcified or ossified Where areas of typical hyaline cartilage are found the lacunar cells are ovoid while in myxomatous areas spindle-shaped and stellate cells are commonly seen. Morton has described the pleomorphism which includes binucleate forms and even true giant cells Numerous mitoses are not often observed Vascularity is quite variable

Central chondroma is the commonest cause of osteolytic tumors of the phalanges. Often they are mistaken for cysts In this location



Fig. 27A Case illustrating danger of roentgen therapy without microscopic diagnosis Appearance of lesion treated elsewhere by roentgen therapy as a giant cell tumor without improvement.

they are consistently benign we have never encountered an exception to this rule although Morton records one case Conservative management of phalangeal chondroma is therefore justified.

Treatment. While we are of the opinion that the only effective method of treatment of chondrosarcoma is surgery a view also expressed by Morton, this does not necessarily imply that amputation



Fig. 27B Appearance 11 months later operation revealed chondromyxosarcoma.

is indicated in every case of chondrosarcoma of an extremity bone. For primary chondroblastic sarcoma amputation is the only safe procedure Conservative measures such as wide resection have a place in secondary chondromyxosarcoma in such bones as the fibula or ulna and may be done widely yet without much greater dis-



A



B



C

Fig. 28. A Chondromyxosarcoma of scapula; partial excision was attempted elsewhere. B Appearance after partial scapulectomy showing recurrence in the glenoid stump. C Appearance after total scapulectomy 5½ years after excision. See also Figure 28D



Fig. 28D Shoulder function more than 12 years after the total scapulectomy patient is still well

ability than is entailed by simple excision of the actual tumor bearing area this holds true for rib tumors as well When such conservatism is practiced great care must be taken in selecting the cases and in completely removing the affected area

Segmental resection of a portion of the shaft of a long bone such as the femur or humerus has been recommended by Phemister (68) who has an impressive group of cases so treated with favorable long term results

Total excision of the scapula for chondrosarcoma has been occasionally followed by a brilliant result. After such a procedure, one of our patients has been well for 12 years with a useful upper extremity—see Figures 28A–D (9a,10a)

In exceptional circumstances, transformation of a benign osteochondroma into a chondrosarcoma presents the opportunity for resection or excision of the tumor through a base of unaffected bone. Figure 19 illustrates such a case The tumor arose in the distal end

of the femur and there has been no recurrence or metastasis for a period of 10 years However it is obvious that such cases are the exception, and that if amputation is to be avoided, experience and the help of an astute pathologist are essential

ENDOTHELIOMA OF BONE (EWING S SARCOMA)

Many of the cases that were designated as "small round cell sarcoma" of bone some 2) years ago are now recognized as belonging to the group of endothelioma or Ewing s sarcoma In 1866 Lücke (55) first described a primary bone tumor resembling endothelioma Sporadic reports appeared thereafter until 1921 when Ewing (28) pointed out the distinct features of the disease which in his opinion warranted considering it as a definite clinical entity It originates chiefly in the shaft of the long bones occurs mostly in children or young adults presents a characteristic roentgenographic and histologic appearance and is unusually radiosensitive

While relatively uncommon this tumor occurs more frequently than is ordinarily realized Next to osteogenic sarcoma it is the most common primary malignant tumor of bone and in a large series of such cases represents about 25 per cent of the total It occurs twice as frequently in males as in females It is a disease of childhood and adolescence most of the cases occur under the age of 25 and the average age is 15 7 years. The disease affects the lower extremity most frequently in the following proportion

Lower extremity	50 per cent
Upper extremity	21 per cent
Ribs	17 per cent
Pelvis	12 per cent

Pain, which becomes more severe at night is predominately the first symptom. Disability follows early and progresses proportionately while demonstrable swelling may not be evident for some time Actual bony swelling due to growth of the tumor occurs early but it is masked by an attendant soft part atrophy of disuse occasioned by disability circumferential measurements are thus apt to be misleading, but careful palpation reveals the true situation. The onset is often insidious, and not infrequently the complaint is of pain distal to the actual level of involvement. It is therefore extremely important, in obtaining the first roentgenograms to insure



Fig. 20 Endothelioma of femur (16b) Originally diagnosed as osteomyelitis on the basis of a biopsy performed shortly after mild roentgen therapy The symptoms persisted the disease progressed, and a subsequent biopsy revealed the presence of endothelioma. Patient died.

adequate exposure of all possible bony sources of the pain. The latter is often intermittent in the early stages with periods of relative quiescence and minimal disability occurring between increasingly more severe prolonged attacks—and so putting the observer off guard—but persistent pain in any bone warrants repeated roentgenographic examination. Only by frequent examinations at regular intervals can we hope to improve our average of early diagnosis with, perhaps, correspondingly improved end results of treatment. Fever and leukocytosis are relatively common at onset although not so marked as in acute or subacute osteomyelitis with which this condition may readily be confused. In fact the differential diagnosis between endothelioma and subacute infection is at times most difficult on clinical, roentgenographic and even microscopic findings (Fig. 29).

The progress of the disease is extremely variable, being very rapid in some instances while in others a fatal termination may be long deferred. In our experience the average duration from the date of admission is 21 months. The disease tends to metastasize not only to the lungs as in osteogenic sarcoma but also to other bones, particularly the skull. Pathologic fracture is not frequent, but may occur relatively early in a weight bearing bone or in a rapidly growing tumor.

While the roentgenograms are usually characteristic, at times the appearance may so closely resemble that of acute infection that microscopic evidence is needed in order to differentiate between them. In the early stages the disease presents an area of rarefaction in the cortex; this rapidly involves the subperiosteum and extends longitudinally to produce an elongated fusiform tumor with patchy destruction of the cortex—described as a "moth-eaten appearance" (Fig. 30)—and with pronounced periosteal reaction giving the lamellated appearance often described as "onion-peel effect." Later reactive radiating spicules may make their appearance in the periosteum (Fig. 31). The diaphysis of the long bones is usually the primary site but occasionally the metaphysis may be the site of origin, or sometimes the flat bones such as the scapula or ilium (in 25 per cent of cases). Metastases are predominately osteolytic. The skull is most frequently the first to be involved.

Endothelioma produces neither cartilage nor bone. Where new bone is found in relation to the tumor it is reactive bone rather than tumor bone; it is indistinguishable from healing or inflammatory

bone and is due to a reparative effort of the bone-forming elements. Degenerating bone surrounded by tumor cells represents destruction of the normal architecture of the cortical lamellae. These processes



Fig. 30. Illustration of the moth-eaten appearance frequently seen in *endothelioma of bone. Its location in* the metaphysis might suggest osteogenic sarcoma.



Fig. 31. Endothelioma occupying a characteristic position in the diaphysis *with fusiform shape* and showing lamellated splitting of the cortical zone.

occurring simultaneously give rise to a characteristic roentgenographic appearance. Ewing originally considered this tumor to be medullary in origin, hence the earlier term "endothelial myeloma," but he later revised this opinion. DeSanto (26) in a comprehensive

survey describes its origin from perivascular lymph spaces in the haversian canals and beneath the periosteum where lymphatic endothelium is definitely known to exist Involvement of the medullary cavity, while prominent is probably secondary

Differential Diagnosis. Benign conditions including cyst fibrous dysplasia chondroma giant cell tumor xanthomatosis are readily differentiated Osteogenic sarcoma occurs at a slightly older age than does endothelioma and is more apt to originate in the metaphysis and later to invade the epiphysis The tumor tends to be pear-shaped rather than fusiform and Codman's triangle of periosteal reflection is rarely if ever observed in endothelioma. Pain is the first *symptom of both conditions and is often referred* but intermittent periods of relative quiescence do not occur in osteogenic sarcoma.

Plasma cell myeloma is readily differentiated by its incidence in the older age groups and the multiple discrete osteolytic areas of skeletal involvement

Reticulum cell sarcoma of bone and metastatic neuroblastoma are frequently extremely difficult to differentiate even on microscopic interpretation The former afflicts an older age group the pain at onset is less severe and the roentgenographic appearance is somewhat different The latter affects the same or a younger age group multiple lesions appear quickly or simultaneously and lymph node involvement is common and early

In acute or subacute infections the fever and leukocytosis are apt *to be higher the pain is usually more sudden in onset* and is acute constant and throbbing, and the local heat and tenderness are more marked However cases have been observed in which the early sections revealed inflammatory tissue without any suggestion of tumor while later in the course of the disease there was unquestioned microscopic confirmation of the existence of endothelioma (Fig. 29) The sedimentation rate, blood culture and response to chemotherapy may prove helpful distinguishing aids

Diagnosis. A definite diagnosis can be made in most cases with careful attention to the clinical history a complete physical and local examination and an adequate roentgenographic survey Microscopic confirmation may then be obtained by aspiration biopsy which is successful in about 80 per cent of cases or by resorting to a formal biopsy Primary wound closure is essential if an open biopsy is carried out, and the surgeon should give due *consideration to the*

importance of obtaining tissue from a representative area to submit to the pathologist

This tumor is highly radiosensitive; in fact, one of the distinguishing features between it and other lesions (notably acute inflammation) is its prompt response to irradiation. Accordingly, the therapeutic test has been recommended as a means of establishing the diagnosis in certain equivocal cases. However, endothelioma is so radiosensitive that even a single exposure to roentgen rays prior to biopsy has been responsible for errors in diagnosis, and the microscopic picture has been so altered that the pathologist was unable to make a correct diagnosis. It is highly desirable, therefore, that pathologic evidence be available either by aspiration biopsy or formal biopsy before any form of therapy is instituted.

Treatment. In treating endothelioma, the method of attack will vary with the site of the tumor and the length of time that the condition has been present. Certainly in such a highly malignant and fatal disease every available means of therapy must be employed. Therefore, it would seem that a combination of irradiation, surgery, and Coley's toxins should be considered, since a review of the literature fails to disclose any 5 year recoveries resulting from the employment of any one of these modalities alone.

Amputation and resection are the two surgical methods available. Many bones lend themselves to a wide resection (Fig. 32A–B) in certain carefully selected cases; the fibula, rib, clavicle, and radius seem best suited for such a procedure. Amputation is required for lesions in the tibia, femur, ulna, and humerus; it should be performed at a level proximal to the bone involved.

The value of Coley's toxins is still much debated and apparently is not yet firmly established. It would seem that the more anaplastic the tumor, the more radiosensitive it is and the more susceptible to the effects of Coley's toxins. It follows that the toxins should be given in every case of endothelioma. This opinion is given support by an analysis made in 1940 of the cases from the Bone Sarcoma Registry in which it was found that 6 of the 11 cases of 5 year survival had received the toxins in addition to other forms of therapy. Further support is given by the fact that 3 of the 4 survivals in our series had adjuvant toxin therapy.

Coley's toxins should be given in every case as a prophylactic measure and not reserved, as has so often been the case in the past,



Fig 32A Endothelioma of fibular shaft (16a)

as a last resort in the hopelessly advanced stages of the disease The injections may be instituted while the patient is receiving roentgen therapy or as is probably preferable immediately upon completion of the prescribed therapy Daily injections given over a period of 2 or 3 weeks in doses increased to the point of tolerance constitute a single course Repeated courses are then given every 2 or 3 months for 3 or more courses depending upon the individual response For details of treatment see page 524 If a resection or amputation



Fig 32B Result 6 years after treatment by preoperative irradiation, resection of involved segment, and stabilization of mortise by means of vitallium screws end result, excellent (10a)

has been done the toxins can be administered postoperatively beginning on the second or third day after operation, and continuing as described above.

Metastases. A most discouraging feature of this tumor is its proclivity for metastasizing to other bones notably the skull the lungs and sometimes to the lymph nodes and viscera as well

The bony metastases are nearly always osteolytic and are often detected clinically by pain and swelling several weeks before the lesions can be demonstrated roentgenographically It therefore seems

worthwhile to administer roentgen therapy whenever and wherever pain and swelling suggest metastases. The secondary lesions are usually not as radiosensitive as the primary but considerable palliation can be achieved until the rapidity of recurrences and new

TABLE XI

Eleven Cases of Endothelioma That Survived Five Years Registered in Bone Sarcoma Registry as of May 1940

Sex	*Bone involved*
Male [illegible] cases	Tibia, 3 cases
Female 3 cases	Fibula 2 cases
Age	Femur 2 cases
Youngest [illegible] years	Humerus 1 case
Oldest 46 years	Scapula 1 case
Average 1[illegible] years (14.1 years if 46 year old patient is omitted)	Jaw 1 case
	Rib 1 case

Interval from onset of symptoms to admission and treatment

Shortest 3 days
Longest 18 months
Average 4 months

Methods of treatment employed

Surgical
- Amputation, [illegible] cases
- Excision or resection, 6 cases (3 preceded amputation of fibula, femur and humerus respectively; 3 without amputation of jaw, scapula, and rib respectively)

Radiation
- Without surgery (also had toxins) 1 case
- Preoperative, 1 case
- Postoperative 4 cases
- Preoperative and postoperative 1 case
- Not stated which, 1 case

Toxins
- Preoperative 1 case
- Postoperative, 2 cases
- Preoperative and postoperative 2 cases
- Without surgery (also had roentgen therapy) 1 case

areas of metastasis make further therapy both hopeless and inadvisable. Even for pulmonary metastases some palliative therapy may be worth considering if the general condition of the patient warrants it. But in any treatment of metastatic lesions moderate palliative doses should be administered rather than the full therapeutic doses designed to eradicate the tumor completely.

When metastases are present, administration of Coley's toxins for a period of several weeks is justifiable. If no improvement is evident

at the end of this time, they should be discontinued and roentgen therapy given to all demonstrable and troublesome foci.

Prognosis. The average length of survival after the disease is first recognized is 21.3 months. There are only a few examples of 5 year recoveries of cases in which the diagnosis was established beyond a doubt (Table XI). Only too frequently metastases are present when the patient first applies for treatment.

Results. In a total of 136 cases treated in the Bone Tumor Department of Memorial Hospital up to the middle of 1947 there were 120 with histologic verification. Of these, 59 were treated prior to 1942 and 55 died of disease in less than 5 years. The 4 proved cases (6.7 per cent) that are alive and well 6, 9, 11 and 13 years respectively, received treatment as follows.

Case No.	Irradiation	Surgery	Toxins
1	\	None	Y
2	\	None	\
3	\	Resection	\
4	Y	Resection	None

PLASMA CELL MYELOMA

The Bone Sarcoma Registry recognizes four types of myeloma: (*1*) plasma cell myeloma, (*2*) myelocytoma, (*3*) lymphocytoma, (*4*) erythroblastoma.

The first type is the one usually encountered while the others are so rare as to constitute pathologic curiosities. All arise from cells normally present in the bone marrow. A microscopic examination is required to differentiate one from the other and the clinical features are essentially similar in all of them.

Rustizky (72) in 1873 was the first to employ the term "multiple myelomata." Since then many reports of multiple bone marrow tumors have appeared in the literature so that the condition is now recognized as a definite clinical and pathologic entity.

It is a relatively rare condition. Geschickter and Copeland (34) estimated that it constitutes 0.03 per cent of all malignant growths. The majority of observers are agreed that the tumor is derived from the blood forming cells of the bone marrow. It is generally accepted that the myelomas appear as multiple primary lesions and do not metastasize by cell transplantation. The tumor is confined to the

bones and in only a few instances has it been described in extra skeletal sites. Metastasis to the lungs rarely occurs.

The condition is characterized by multiple bony foci and is found chiefly in men between the ages of 40 and 60. In 68 cases studied at Memorial Hospital there were 51 men and 17 women, the average age was 51.4 years. It is manifested by deep-seated pain in the bones, characteristic deformities of the skeleton, severe secondary anemia and emaciation, and spontaneous fractures in many bones of the body. In fact, pathologic fracture of a rib as a first symptom is said to be pathognomonic for plasma cell myeloma.

The bones involved are those with red marrow, notably the vertebrae, sternum, ribs, clavicles, skull, scapulas, and ilium. The marrow in the ends of the long bones of the extremities is relatively seldom affected.

Pain is invariably the most constant, the earliest, and often the only symptom complained of. The pain at first may be variable and generalized; it is usually worse in the daytime and is accentuated by movement. It is subject to remissions and acute exacerbations; while at first it may be intermittent and wandering, eventually it becomes intense and unremitting. Backache or thoracic pain may indicate early involvement of the vertebrae or ribs, and shortening of stature and paraplegia may be early symptoms. Progressive weakness, increasing anemia, and continued low blood pressure may be concomitant symptoms. Herpes zoster may appear later, and anorexia is usual as the disease progresses. Spontaneous fractures are common, and occur in about 62 per cent of all cases. Sudden unexplained pain in the ribs or spine in a man over 40 years of age should arouse suspicion of a partial collapse of a vertebra or of a pathologic fracture of a rib due to myeloma.

Roentgenographic Features. The most characteristic feature of this disease is the presence of multiple discrete areas of radiolucency in the bone. The skull and other bones show sharply punched-out areas which vary considerably in size (Fig. 33). Within the tumor the absorption of bone is complete, producing a sharply demarcated rounded central area with no evidence of bone production (Fig. 34). There is no condensation at the periphery and no periosteal reaction as a rule. Solitary lesions have been known to exist for a time and to have been of greater size than usual. However, multiple lesions eventually appear, and a complete skeletal survey is indicated in all



Fig. 33. Typical cranial involvement seen in plasma cell myeloma.

cases suspected of being myeloma (Fig. 35) The tumor growth replaces the marrow and frequently so erodes the bony structure as to cause deformities of various sorts, with or without spontaneous *fracture*.

Chemistry The presence of Bence-Jones proteinuria is strongly suggestive of this disease. It occurs in about 40 per cent of all cases, although it may be present in other conditions such as leukemia Hodgkin's disease, or metastatic cancer of bone Hyperproteinemia is sometimes one of the most striking concomitants of this disease, and its presence should always make one suspicious of myeloma. A marked increase in the total protein of the serum is of value in



Fig. 34. Solitary plasma cell myeloma in the midshaft of humerus. Multiple involvement became manifest $1^{1}/_{2}$ years later



Fig. 35 Plasma cell myeloma with multiple involvement of humerus, scapula, ribs and many other bones This patient survived for 11 years after onset of symptoms due to the original focus in the neck of the femur

confirming the diagnosis of plasma cell myeloma It is found in at least half of the cases There is usually an increase in the globulin fraction and an inversion of the albumin–globulin ratio The alkaline phosphatase content of the serum is normal or slightly elevated in this disease while the calcium and inorganic phosphorus are frequently definitely increased and may even be very high The acid phosphatase is always normal—an important point in the differential diagnosis of metastases from prostatic carcinoma The sedimentation rate is consistently increased so that a normal reading is strong presumptive evidence against plasma cell myeloma

Diagnosis. The diagnosis of this condition is based on the history of vague bone pains in an individual over 40 years of age, or with any acute onset of thoracic or vertebral pain due to pathologic fracture. The roentgenograms reveal multiple punched-out areas in the skull, ribs and other bones and the laboratory studies of the blood and urine are often confirmatory

Aspiration biopsy from a typical lesion is usually successful and should be attempted or a formal biopsy may be taken from a rib or other involved bone Sternal marrow puncture is a simple diagnostic procedure and is usually indicated It is preferable to a formal biopsy and may be equally informative.

Differential Diagnosis. In the differential diagnosis many conditions involving bone must be considered. Among these are hyperparathyroidism (Fig. 36) metastatic cancer involving bone osteogenic sarcoma, adrenal neuroblastoma endothelioma osteitis deformans, and osteomalacia. The age of the patient, the blood chemistry studies, and the results of sternal marrow puncture and aspiration biopsy will usually suffice to differentiate these condition. The presence of Bence-Jones protein in the urine and the absence of any demonstrable primary tumor or pulmonary metastases may be helpful.

Treatment. The treatment of this condition is not at all satisfactory Roentgen therapy may have a temporary albeit worthwhile palliative effect. It should be moderate in amount and not repeated often in the same area. Indiscriminate irradiation of large areas with huge doses serves to increase the difficulty under which the mechanism forming the red cell is laboring. When there are multiple lesions only those areas giving rise to symptoms should be treated Support of the spine or pelvis by appropriate braces and of the long bones



Fig. 38. Osteitis fibrosa cystica generalisata (Recklinghausen's disease) due to hyperparathyroidism. Note destructive changes and thinning of cortex, similar to that seen in plasma cell myeloma.

by splints may prevent, postpone or relieve pathologic fracture Snapper (77) reports appreciable relief of pain from stilbamidine or pentamidine given in combination with a diet low in protein. The drug is administered daily or every other day for a total dosage of 4 to 6 Gm. Myeloma cells Bence-Jones proteinuria, and high blood globulin levels persist, but in most treated cases pain is alleviated. While the disease may not be cured it may thereby be arrested

Prognosis. Cures of unquestioned cases by any method of treatment are exceedingly rare if, indeed they ever occur Survival periods vary from 6 to 18 months The average duration of life is 1 year although a rare case may continue under observation and treatment for 5 or 6 years In the 48 cases at Memorial Hospital that died of the disease the average period of survival from the time of admission to death was only 7.5 months

Results. Despite treatment this disease is uniformly fatal. Roentgen therapy and stilbamidine may relieve the symptoms temporarily but probably do not prolong life One of our patients is alive with extensive disease 11 years after the diagnosis was estab lished by bone biopsy for what was then considered to be a solitary lesion It is probably an example of late generalization of the disease (Fig 35) Such instances are very rare.

RETICULUM CELL SARCOMA OF BONE

In 1939 Parker and Jackson described reticulum cell sarcoma of bone as a specific disease entity based on an analysis of 17 cases and the Bone Sarcoma Registry has accepted the term in their revised classification of primary bone tumors Many of these tumors in the past were termed "round cell sarcoma" and later endothelioma " but their clinical behavior, roentgenographic features and response to therapy set them apart from other types of primary bone tumors They are to be distinguished from reticulum cell lymphosarcoma—a disease having its inception in lymph nodes and not infrequently metastasizing to bone The type cell is identical, but the tumor arises primarily in bone and occasionally metastasizes to lymph nodes later in the course of the disease.

This condition may be seen at any age. It usually occurs in the long or flat bones and in spite of extensive involvement, leaves the patient in good general condition. Fever is seldom present. Pain is

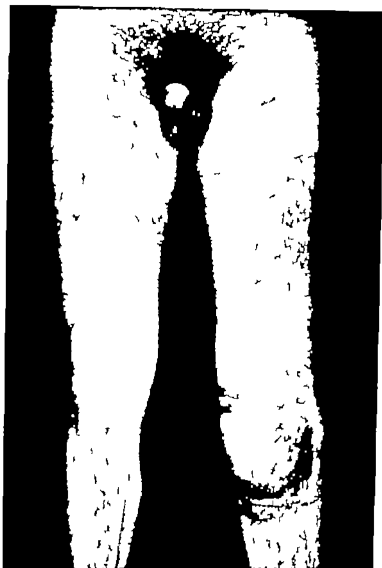


Fig 37 Reticulum cell sarcoma of upper tibia, with secondary mass in left groin due to lymph node metastasis.

predominately the initial symptom. It usually points directly to the zone of involvement, and is rarely referred from a lesion higher up The pain is relatively sharp and steady and is not relieved by rest. Accessible bones show some swelling early while in deep-seated bones swelling may not be manifest until quite late Disability

ensues early and increases steadily As a result, the patient usually seeks advice in the early phases of the disease and roentgenographic studies are generally clearly indicated On the other hand a few cases have been described with a slow insidious onset of vague pain with indefinite localization and minimal disability continuing until a pathologic fracture several months later prompted roentgenographic studies leading to the diagnosis

The disease is more frequent in youth and early adult life the average age being 29.2 years Men are more commonly affected than women in the proportion of 5 3 The long bones such as the tibia femur humerus and ribs or the flat bones such as the scapula ilium or sternum are the bones usually involved the skull is rarely if ever involved either primarily or with metastasis in contradistinction to endothelioma. Metastases may occur to regional lymph nodes or occasionally to the lungs (Fig. 37)

Roentgenographic Features. These features may sometimes be difficult to interpret but usually are fairly characteristic The appearance of "cracked ice in a glass" is a reasonably descriptive analogy that suits most cases (Fig. 38A–B) The lesion i osteolytic medullary and cortical destruction predominates while bone production or periosteal reaction is minimal (Fig. 39) Extension usually takes place in the long axis of the bone and extraosseous involvement is rarely observed until later in the course of the disease The metaphysis is the usual site of origin but a spread into the diaphysis is usual or even into the epiphysis

Pathology The re iculum cell sarcoma is composed of sheets of cells with round ovoid or indented nuclei which are nearly twice as large as those seen in endothelioma When stained to bring out the reticulum this is found running in delicate threads and strands around groups of tumor cells and also between individual cells

Aspiration biopsy is frequently successful in confirming the diagnosis However if there is any doubt as to the exact diagnosis a formal biopsy is definitely indicated and carries no hazard with its performance if carefully done

Differential Diagnosis. In the differential diagnosis one must consider endothelioma, the generalized form of reticulum cell lymphosarcoma, osteogenic sarcoma and inflammatory lesions particularly syphilis Attention to the history the age of the patient the location in bone and mode of spread the roentgenographic appearance and finally the microscopic examination should establish the diagnosis in the vast majority of cases



Fig. 38A. Reticulum cell sarcoma of bone in a 21 year old woman.



Fig. 33B Appearance 1 year later after treatment with high voltage roentgen rays and Coley's toxin. Patient has been symptom-free and without evidence of disease for $2^{1}/$ years.



Fig. 30 Reticulum cell sarcoma of bone in an early stage

Treatment. Parker and Jackson stated that the best treatment probably was early diagnosis by biopsy followed by immediate amputation and irradiation. Subsequent experience, however, inclines us to the view that the loss of an involved extremity might well be avoided. This tumor is highly radiosensitive and adequate irradiation along the lines described for endothelioma would seem to be the method of choice. In the light of our present knowledge a total tissue dose of 3,000 to 3,500 r units should be the aim. While this irradiation is being given, or immediately thereafter, Coley's toxins



Fig 40. A Reticulum cell sarcoma of bone in a 17 year old boy B Appearance 7 years after treatment by irradiation and Coley's toxins patient has been free of disease for 14 years

should be administered as described on page 524 If a recurrence should take place for which further irradiation cannot be administered because of the local skin tolerance a wide local resection or an amputation may then be carried out When there is definite or suspected regional lymph node involvement carefully planned irradiation to such areas is indicated

Prognosis. In spite of its apparent highly malignant nature—as evidenced by the clinical roentgenographic and pathologic aspects—reticulum cell sarcoma of bone is more than usually amenable to appropriate treatment If a case is seen and treated early before metastases are demonstrable the outlook for a long term survival is rather favorable (Fig. 40) Of the 12 cases treated at Memorial Hospital 5 or more years ago 6 have survived for 5 or more years.

Results. The results of treatment of 24 cases of reticulum cell sarcoma of bone at Memorial Hospital are as follows

Total number of proved cases	24
Number treated prior to 1942	12
Number alive and well over 5 years	6 (or 50 per cent)

LIPOSARCOMA OF BONE

There is a possibility that another type of primary malignant bone tumor exists which derives from the fat tissue of bone marrow. While as yet it is not convincing, there is some evidence that primary liposarcoma of bone is a new and distinct disease entity. So far, 4 such cases from Memorial Hospital have been described and 3 others have appeared in the literature.

In 1931 Stewart (79) made a rather strong case for the marrow fat origin of certain unusual pseudoepithelial spindle or polyhedral cell diffuse or alveolar tumors of bone. However he freely admits that their derivation from fat tissue cannot be proved, nor was there evidence that these tumors were metastatic or that they invaded bone from without.

From the few recorded cases it appears that the tumor may occur at any age, is quite osteolytic and may arise in one or several bones. Its course differs from that of other types of bone sarcoma, and this should be borne in mind when giving a prognosis. A guarded but not necessarily hopeless outlook is justified.

The tumor is relatively radiosensitive and probably treatment by high voltage roentgen rays in total tissue doses approximating 4 000 to 5 000 r units merits consideration. Amputation may prove curative and is indicated if irradiation fails to control the growth. Pulmonary metastases if they occur should also be treated by irradiation since the metastases also appear to be relatively radiosensitive.

It is desirable that cases of a similar nature be studied and reported in detail so that our knowledge of this rare tumor of bone may be increased and its true nature more fully understood.

Metastatic Carcinoma

Theoretically it is possible for any primary malignant tumor to metastasize to bone and this thought must be constantly borne in

mind whenever a patient who has been treated for a malignant growth complains of pain in a bone or joint. Actually, some forms metastasize more commonly than others the most frequent sites of

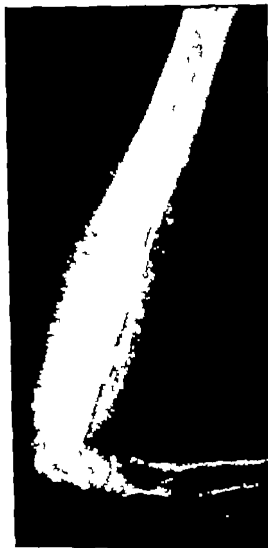


Fig 41 Metastasis from teratoma testis. This occurs only rarely

origin are the breast, thyroid kidney and prostate Less common sites are the stomach, lung, and uterus and in rare instances, the parotid, testicle (Fig. 41) pancreas and other organs. According

to Kitain (52) 10 per cent of all types of carcinoma develop skeletal metastases

Numerically the incidence of metastatic involvement of bone probably approximates the number of cases of primary malignant bone disease and the condition is certainly of paramount importance from the standpoint of diagnosis and treatment. With increasing reliance on routine roentgenographic examinations particularly when bone pain is complained of this condition is being more frequently diagnosed and its confirmation and classification is rendered more reliable as the use and popularity of aspiration biopsy increases

Spread of malignant disease to bone can occur as a result of direct extension of an overlying soft tissue tumor True metastasis can take place either *through the blood stream or by retrograde lymphatic* channels The hematogenous route may give rise to deposits in any of the bones The skull, ribs spine, and pelvis, as well as the femur and humerus are favorite locations The bones of the hands and feet *are rarely* involved. With *retrograde lymphatic extension the bones* near the primary growth are naturally more liable to invasion thus in mammary cancer the ribs, thoracic spine and skull are the favored sites while in prostatic cancer the sacrum, pelvis and lumbar *spine are commonly affected*

Most bone metastases begin in the spongiosa and are therefore marrow metastases Cortical lesions are infrequent although as a central medullary area progresses it extends to invade cortical bone.

Patients with metastatic tumors of bone may remain singularly free from symptoms but as a rule pain is the most constant and troublesome complaint. It depends largely upon the bone involved, the location in the bone and the rate of tumor growth Thus in *weight bearing portions of the skeleton* or where there is muscular stress pain is apt to manifest itself earlier and to be more severe As the lesions are usually central swelling is not apt to be an early feature but disability ensues early especially when the weight *bearing bones are* involved In advanced cases, pain may become intolerable and require increasingly larger doses of opiates

Not infrequently the first intimation of the existence of a carcinoma of the thyroid kidney prostate etc is the subjective as well *as objective* evidence of a metastatic lesion in bone Microscopic examination of a biopsy specimen from such a lesion may yield a diagnosis of metastatic cancer and impel a renewed search for the

primary lesion At times, the origin of the metastatic tumor can be detected in such biopsy material but we have known instances where even an exhaustive search at autopsy failed to reveal the site of origin of some metastatic tumors

Signs Too great importance cannot be placed upon the need for early roentgenographic examination when a patient known to have been treated for a carcinoma complains of bone or joint pain Visible and palpable physical signs of metastases may be notably absent, and sole reliance must be placed on the interpretation of the roentgenograms Pathologic fracture may be the first sign to suggest the presence of metastasis it may follow a trivial injury or occur spontaneously Secondary anemia weight loss, and cachexia often appear as the disease progresses

Roentgenographic Features. In every instance where bone metastasis is suspected a complete skeletal roentgenographic survey should be carried out in addition to detailed studies of symptomatic areas Only in this way will multiple lesions many of which may be quite asymptomatic be demonstrated. Early lesions may be difficult to detect and may require the expert opinion of a competent roentgenologist. Any alteration in bone density at the site of subjective pain should arouse suspicion of metastasis particularly in an individual over 30 years of age or in whom a definite primary tumor is known to exist. If more than one such area is revealed in the skeletal survey suspicion gives place to presumption. Solitary lesions may exist for some time but as a rule other areas of involvement will sooner or later make their appearance

The area of involvement in the long bones is usually in the region of the nutrient artery On the roentgenogram, the lesions generally appear osteolytic They are irregular in outline and central or medullary and rapidly extend to destroy the cortex tending to early pathologic fracture The osteolytic metastases are frequently found in cases of renal or thyroid carcinoma. In the former they are spotty and the outline of the bone appears to be erased. In the latter there is an expansile tendency with a cystic or soap bubble appearance Metastases from prostatic or breast carcinoma on the other hand, are very often osteoblastic but osteolytic areas may also be found in the same patient (Fig. 42)

If the primary tumor is not known complete roentgenographic studies are indicated. Pyelograms may demonstrate a primary renal tumor A chest film may reveal a primary lung tumor A complete

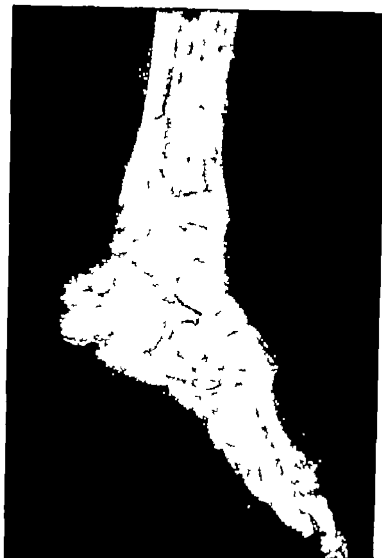


Fig. 42 Multiple osteoblastic metastases of carcinoma of breast.

gastrointestinal series may disclose a primary lesion in the esophagus, stomach small or large bowel etc

Differential Diagnosis. When the presence of a primary malig nant tumor is known, the diagnosis of metastatic bone involvement is usually not difficult One or more osteolytic areas in bone sometimes associated with osteoblastic areas, are readily discernible on

roentgenographic examination when attention is directed to the involved site by pain in the area. However, when solitary lesions exist, or there is no demonstrable primary tumor, diagnosis may be extremely difficult If after a thorough investigation including clinical laboratory and roentgenographic study, the diagnosis of a suspected bone lesion cannot be determined, a biopsy is justified. Aspiration biopsy may be of great value if unsuccessful a formal biopsy from a representative area should be done. While in some cases no primary cancer can be disclosed, and even autopsy may fail to establish the source of the metastases a competent pathologist can usually determine from biopsy material whether the lesion is primary or metastatic and if metastatic its origin from kidney, breast etc

The age of the patient is of assistance in the diagnosis, as metastatic cancer is rare in persons under 30 and primary bone sarcoma is uncommon after that age. Plasma cell myeloma affects the same age group but sternal marrow studies an elevated serum protein and the presence of Bence-Jones proteinuria in the absence of a demonstrable primary tumor readily differentiate the two conditions The lipoid granulomas are readily excluded as they affect a younger age group and the symptoms are less severe

Blood chemistry studies are very helpful. A high calcium and phosphatase and a low phosphorus content distinguish the multiple osteolytic lesions of hyperparathyroidism An elevated-serum protein indicates plasma cell myeloma. An elevated acid phosphatase is practically pathognomonic of prostatic metastases to bone

General Principles of Treating Metastases in Bone

Treatment is purely palliative. In view of the ultimate prognosis which is uniformly bad treatment of bone metastases should be directed toward relief of symptoms for as long a period as possible The measure of temporary success depends on the radiosensitivity of the tumor Considerable relief for varying periods may be obtained in anaplastic and radiosensitive tumors by a carefully planned program of irradiation. Roentgen therapy is given to the symptomatically involved areas but in smaller amounts than would be employed in treating a primary tumor in the same location, the object being to attain palliation and not a cure In about 25 per cent of the cases

relief of pain and objective improvement in the appearance of the films of the bone areas are obtained such cases seem to enjoy a definite prolongation of life as a result of the treatment. Irradiation therapy, on the other hand, may add to the patient's distress rather than alleviate the symptoms. Therapy must therefore be employed with caution and discrimination.

Pathologic fracture must be guarded against and suitable braces or supports provided where appropriate. When pathologic fractures occur they are cared for along the same general principles as are employed for nonpathologic fractures.

Endocrine preparations and radioactive isotopes have been used in the treatment of certain selected cases, but both are of recent development and results are still inconclusive although encouraging.

Specific Types of Metastatic Cancer

From Carcinoma of the Breast. Cancer of the breast is probably the most important source of osseous metastases occurring in 25 to 35 per cent of all cases. Kauffmann (51) found at autopsy that in roughly two-thirds of all cases of breast cancer there were bone metastases. At times, the metastatic lesions give rise to symptoms and are discovered even before the lump in the breast is noted. On the other hand, they may appear at any time after treatment for the primary breast cancer.

In mammary cancer the ribs, thoracic spine, and skull are favored sites for metastases. By the time definite complaints of bone pain are made, the alteration in the bone architecture is usually sufficient to be detectable on the roentgenograms. The early lesions are usually purely osteolytic (Fig. 43) but subsequently and particularly after specific treatment, many of the bone lesions may appear osteoblastic so that it is not uncommon to find an association of osteolytic and osteoblastic lesions in the same case (Fig. 44).

Ovarian sterilization effecting withdrawal of the ovarian hormone has been extensively employed in recent years for metastatic breast cancer. Striking benefits have been noted in cases with bone invasion although there seems to be no effect on soft part and visceral involvement. Such sterilization is mainly effective in young patients. It can be accomplished surgically or preferably by the standard roentgen ray sterilizing pelvic cycle. Areas of bone destruction may

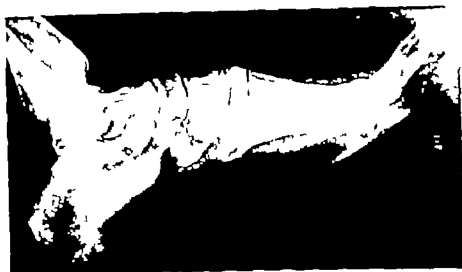


Fig. 43. Carcinoma of breast with osteolytic metastasis to the os calcis. Involvement of the bones of the hands and feet is rare.

be partially or completely regenerated (Fig. 44) and general physical improvement is manifested by better appetite, gain in weight, and a feeling of well being.

The administration of testosterone propionate has recently received a rather thorough test. Many of the patients with bone metastases from breast cancer experience a varied measure of relief from pain. Moreover there is some increased calcification in the osseous lesions for variable periods of time. Because of the danger of hypercalcemia, frequent blood chemistry assays should accompany the clinical treatment. It would seem then that the younger patient should be sterilized at the earliest sign of metastasis if not prophylactically after radical mastectomy while the older patient with symptomatic bony metastases should be treated with testosterone propionate.

From Carcinoma of the Prostate. Kauffmann found at autopsy bone metastases in roughly half of all cases of prostatic cancer. Cancer of the prostate may arise insidiously and spread to the pelvic bones and spine causing dull aching pain, before there are any noteworthy symptoms referable to the primary growth. The sacrum, pelvis and lumbar spine are commonly affected in prostatic cancer. Areas of increased density in the bones in a male patient within the



Fig. 44. Carcinoma of breast Above, multiple osteolytic metastases. Below marked osteoblastic response to irradiation of pelvic area which produced permanent artificial menopause.

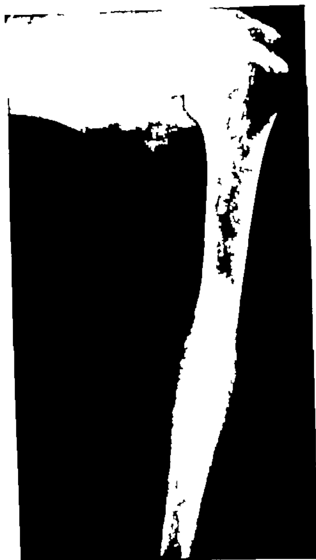


Fig 45. Unusual appearance of metastasis from carcinoma of prostate

cancer age should suggest the possibility of cancer of the prostate, and clinical and laboratory studies should be made without delay A relative increase in acid phosphatase is a reliable indication of metastatic prostate cancer although it is not invariably present. As a rule the bone lesions are osteoblastic (Fig 45) In advanced cases

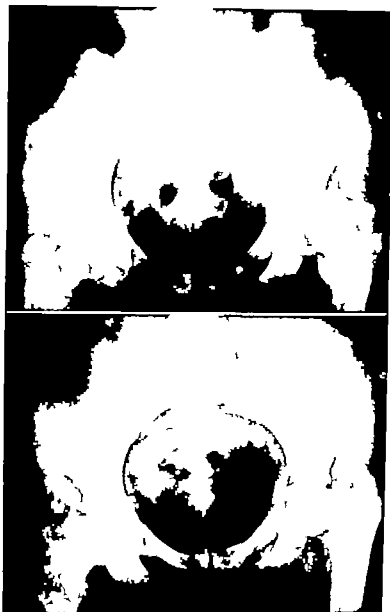


Fig. 44. Carcinoma of breast. Above multiple osteolytic metastases. Below marked osteoblastic response to irradiation of pelvic area which produced permanent artificial menopause.



Fig 45 Unusual appearance of metastasis from carcinoma of prostate.

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the bones are diffusely mottled with small areas of increased density which give a characteristic snowflake appearance

The effect of hormones on prostatic cancer has long been observed and much experimental work has been carried out to date Huggins (45) work on orchiectomy and prostatic cancer is noteworthy

It is doubtful if hormonal therapy can produce permanent cures but this in no way detracts from its importance as a useful additional method of affording palliation, which in some cases is dramatic and long-sustained.

Dean (25) reports that 90 per cent of patients with prostatic cancer metastases are relieved of symptoms for 1 year by orchiectomy and 30 per cent of these for more than 1 year A similar effect, though less rapid is obtained with estrogenic therapy

From Carcinoma of the Thyroid. Thyroid carcinoma may give rise to bone lesions in the skull spine and pelvis For some unaccountable reason the pelvis seems particularly prone to involvement (Fig. 46) Such tumors are bulky and osteolytic destroying a large portion of the bone and expanding to produce readily palpable bone tumors that tend to early pathologic fracture When solitary they may simulate central medullary osteogenic sarcoma, aggressive giant cell tumor or plasma cell myeloma Aspiration biopsy is relatively easy and in a large proportion of cases leads to a definite diagnosis

If the primary thyroid tumor has not been removed it should be excised when osseous metastases make their appearance because if left it will no doubt continue to disseminate tumor emboli.

Roentgen therapy has proved of distinct value in the treatment of involved areas in bone.

A recent trend which warrants considerable future development is the use of radioactive iodine in the treatment of thyroid cancer with metastases to bone Tentatively it would appear that metastatic lesions which produce colloid will in some instances, pick up radioactive iodine selectively This can be determined by administering a small tracer dose of the substance and measuring its distribution with the Geiger counter Suitable cases may then be given therapeutic doses in amounts and at intervals depending upon the individual response Encouraging early results have been obtained to date, but the method is too new to permit of any observations over a prolonged period or definite conclusions as to its ultimate value



Fig. 46. Metastasis to ilium from primary carcinoma of thyroid (10)

From Hypernephroma. Hypernephroma is frequently complicated by skeletal metastases which are few in number and often solitary. In many instances they attract attention before the primary tumor is discovered. When seen as a solitary lesion it may resemble osteogenic sarcoma, angiosarcoma, or endothelioma (Fig. 47). Aspiration biopsy greatly facilitates the diagnosis and may point the way to investigation of the genitourinary tract. However in some cases microscopic examination may present considerable difficulty and the condition may be confused with hemangioendothelioma. If metastasis is solitary or not too generalized removal of the primary tumor is probably the wisest procedure followed by roentgen therapy to the involved bone areas. Pathologic fracture is fairly frequent and must be guarded against.



Fig. 47 Metastasis from carcinoma of kidney

From Carcinoma of the Lung. Bronchogenic carcinoma gives rise to bone metastases which are osteolytic in type with little tendency to produce reactive bone. Peculiar to this type of tumor is the unusual location of the involvement in bone. The lower humerus, midfemur, upper tibia or the clavicle on the side opposite to the involved lung are the favored locations (Fig. 48).

Formerly these tumors occurring in bone were incorrectly interpreted as *primary* since they are frequently solitary and the lung tumors were regarded as pulmonary metastases. Better facilities for *diagnosis in recent years have revealed the true picture.* According to Pool and LaDue (71) in 153 consecutive patients with bronchogenic carcinoma who were followed until they had died of the disease 66 or 43 per cent, showed metastases to the bones demonstrable by roentgenogram or at autopsy.

From Carcinoma of the Gastrointestinal Tract. While skeletal metastases from primary tumors of the gastrointestinal tract are uncommon, this source must be considered when bone lesions are



Fig. 48 Metastasis from bronchogenic carcinoma

encountered and an undetermined primary cancer is suspected In 507 cases of cancer of the gastrointestinal tract including the stomach esophagus, rectum, gallbladder pancreas liver and pharynx, that came to autopsy, Müller (60) found that 5 6 per cent had metastases to bone.

There are hardly sufficient cases to establish any criteria as to the roentgenographic appearance, usual symptoms bones involved, etc., but the incidence is high enough to warrant serious consideration when bone lesions are found which suggest metastatic origin (Fig 49)

From Adrenal Neuroblastoma. This is a highly lethal disease of childhood which is frequently associated with secondary deposits in bone. The tumors arise from the parent cell in the adrenal medulla, the neuroblast or occasionally in some other portion of the sympathetic nervous system. Two varieties are recognized the Pepper (66) form and the Hutchinson (46) form. The former occurring in children under 2 years of age runs a rapidly fatal course, with liver



Fig 49 Metastasis to skull from carcinoma of stomach

and retroperitoneal tissue chiefly affected. The Hutchinson form which presents marked skeletal manifestations is seen more frequently between the ages of 2 and 7 Cranial deposits produce exophthalmos gradual skull expansion, and diastasis of the sutures The lesions in the long bones are purely destructive and occupy a diversified location (Fig 50) It is sometimes difficult to distinguish this condition from endothelioma both roentgenographically and on examination of microscopic sections The metastases are radiosensitive and there are instances in which tumors have markedly decreased in size following a course of treatment with Coley's toxins. Therefore, when this condition is diagnosed the child should be treated with both agents

From Hodgkin's Disease and Lymphosarcoma. Bone involvement in the lymphomatoid group (Hodgkin's disease and lymphosarcoma) is probably more usual than is suspected Not infrequently the principal lesions are osseous and the lymphadenopathy is less prominent. Marrow involvement is probably a constant feature of

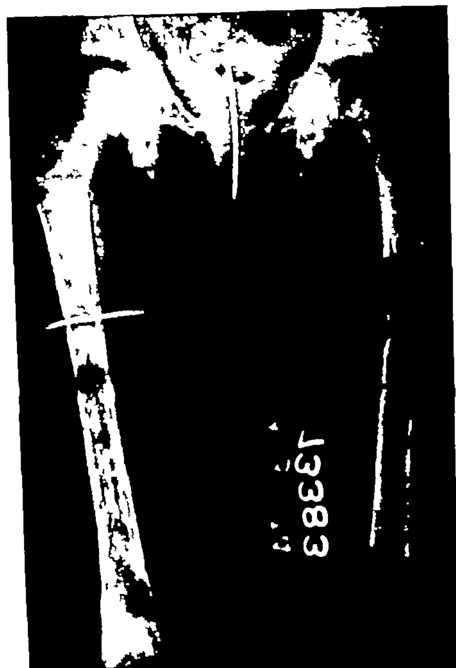


Fig 50 Metastatic neuroblastoma in a 6 year old girl. Practically every bone in the skeleton was affected.



Fig 49 Metastasis to skull from carcinoma of stomach.

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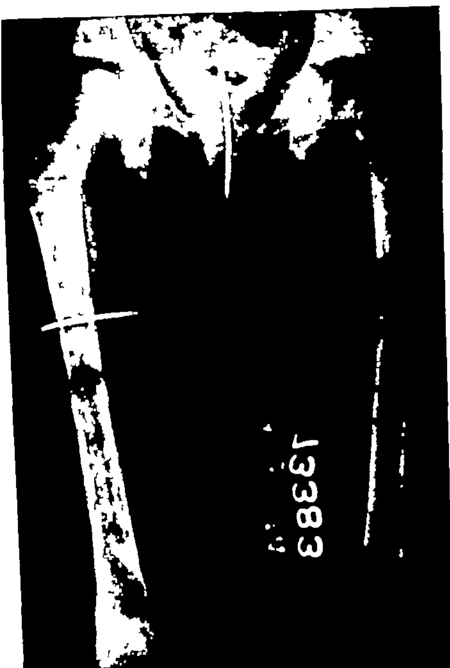


Fig. 50. Metastatic neuroblastoma in a 6 year old girl. Practically every bone in the skeleton was affected.

Hodgkin's disease at least in the later stages but is not readily detected in the roentgenograms However when the spongiosa is involved or when there is cortical destruction roentgenographic interpretation should not be difficult. The presence of sternal pain and tenderness is highly suggestive of skeletal involvement in Hodgkin's disease or lymphosarcoma, but it may also be associated with plasma cell myeloma The bone lesions may be osteoblastic osteolytic or a combination of both. While pathologic fracture may occur, a collapse of the involved vertebrae is rare in Hodgkin's disease in contradistinction to lymphosarcoma and other types of metastatic cancer As in other forms of metastatic bone disease palliative roentgen therapy in moderate dosages is given to all symptomatic lesions

From Sarcoma. The sarcomas are less apt to metastasize to bone than are the carcinomas However soft part sarcomas, such as neurogenic sarcoma and lymphosarcoma may invade bone by direct extension.

Ewing's sarcoma (endothelioma) has a predilection for skeletal metastasis. It is rare to see a case that progresses to its usual fatal end without the appearance of multiple foci in the skull pelvis and other bones Reticulum cell sarcoma of bone may occasionally metastasize to other bones but osteogenic sarcoma rarely if ever does so

Treatment by Bacterial Products. Coley's Toxins

For more than 300 years it has been known that certain bacterial infections particularly erysipelas have been responsible on various occasions for the marked regression of malignant neoplasms in humans. Busch (6) in 1866 was apparently the first to publish an account of this effect. During the succeeding 25 years he was followed by many others who published their observations Various theories were offered regarding the mechanism by which these striking effects were produced but as yet no convincing explanation has been advanced. In recent years Shwartzman (75) Shear (74) Duran Reynals (27) and others have demonstrated that certain bacterial products will induce hemorrhage edema, and even necrosis of the tumors, when injected systemically into tumor bearing animals.

After the causative organism of erysipelas had been discovered by Fehleisen (32) in 1881, it was natural that the sporadic results achieved by accidental attacks of erysipelas should prompt investigators to inoculate patients suffering from malignant disease with the living cultures of Streptococcus erysipelatis Fehleisen himself was the first to do it (1882) in the same year Winslow (80a) also attempted it, and was followed by Holst (44) in 1888 and Kleeblatt (53) in 1890

These experiments were unknown to William B Coley whose interest in the phenomenon was aroused by a case of thrice recurrent inoperable lymphosarcoma of the neck that had recovered after an accidentally acquired erysipelas infection at New York Hospital in 1884 the patient was free of disease in 1891 when Coley first heard of him. Following this observation Coley (21) searched the literature and found records of 38 cases with coincidental malignant disease and accidental or therapeutically induced erysipelas In April 1891 he first attempted to produce an attack of the disease in 10 cases of inoperable malignant neoplasms But the difficulties encountered and the dangers incident to inoculating patients with living cultures led him to substitute killed cultures and in 1892 he added the toxins of Bacillus prodigiosus (Serratia marcescens) This combination has been retained ever since and is known as "Coley's mixed toxins"

Shear (74) has been a tireless investigator in this field and has isolated an active fraction, a polysaccharide from Serratia marcescens which he believes is 1,300 times more powerful in its tumor hemorrhage production than the commercial product that was available in 1943

For the past 50 years numerous reports from investigators here and abroad have appeared expressing favorable or unfavorable opinions as to the effectiveness of the toxins. For a comprehensive analysis of this material and a complete bibliography the reader is referred to the review by Nauts Swift and Coley (61)

Despite these publications and personal communications regarding sporadic examples of remarkable regressions and even of apparent cures, the actual value of the method is still undetermined and in our opinion it is most difficult to evaluate.

Our experience has been limited almost entirely to the preparation made by Parke Davis and Company since 1921 We have used it

extensively during the past 26 years but its merits are difficult to evaluate since in most instances other methods, i.e. surgery irradiation or a combination of both were used in addition to toxins.

In a series of 44 consecutive cases of Ewing's sarcoma treated between 1935 and 1940 there were 6 who survived for 5 years or longer In 4 of these the diagnosis was confirmed microscopically while in 2 it was based solely on clinical and roentgenographic evidence, thus laying these cases open to question. Toxin therapy was given 5 of these patients while the sixth had a streptococcus empyema following a rib resection that had been preceded by irradiation. However it should be noted that all but 9 of the 44 cases received toxin treatment.

During the same period (1935–1940) there were 125 cases of osteogenic sarcoma treated Of these 82 received no toxins with 12 surviving for 5 or more years or 15 per cent another group of 43 cases received toxins, with 11 surviving 5 or more years or 25 per cent.

We have reason to believe that in reticulum cell sarcoma the toxins have yielded the most impressive results when employed with roentgen therapy to the primary lesion. One of the few extraordinary cases is that of Christian and Palmer (8) in which an extensive recurrent reticulum cell sarcoma of the tibia with multiple metastases was treated solely with toxins in large doses over a considerable period of time. This treatment resulted in a complete disappearance of all lesions and the patient is alive (21 years thereafter)

In many cases the toxin treatment has been withheld until the disease has reached an advanced or hopeless stage and then administered for brief periods only It would seem justifiable to start the toxin treatment at an early stage and to withhold other methods (surgery or irradiation) until one could determine definitely the effect of the toxins in that case It is needless to add that in every case microscopic confirmation of the diagnosis should be obtained before starting treatment.

Methods of Administration. (1) Toxins should be kept in a refrigerator and not used beyond the specified date of expiration (2) Dilution should be by sterile isotonic saline solution (3) A tuberculin syringe graduated in half minims is essential for accurate measurement. (4) Dosage for *intravenous* injection is as follows

Dose	Minim
First	1/[illegible]
Second	1/[illegible]
Third	1/[illegible]
Fourth	1/[illegible]
Fifth	1/[illegible]
Sixth	1
Seventh	2
Eighth	3
Ninth	4
Tenth	5

The need for increasing the dose is dependent upon the reaction (chill and fever) produced by the preceding dose. The aim should be to produce a profound constitutional reaction with chill lasting for 15 to 30 minutes and a temperature elevation to 104 to 105 F Children require smaller initial doses and a more gradual increase in the subsequent doses Each case must be treated individually The reactions must be ascertained by frequent recordings of temperature pulse rate and blood pressure until these have reached preinjection levels We have abandoned the intramuscular route as being painful slow in absorption, and less effective in producing reactions. (5) If the patient s condition permits one should give daily injections until a total of 12 to 15 have been given. (6) The diet should be liberal. The patient should always be ambulatory between injections other factors permitting. Anemia should be treated with transfusions and hematinics Vitamin intake at normal levels should be assured. (7) If, after 2 or 3 weeks of treatment, no beneficial effect has been noticed by the patient or the physician, it is usually best to discontinue the injections. If there has been improvement, a continuation of toxin therapy seems indicated.

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AUTHOR INDEX

Italic numbers are used for pages on which bibliographic references occur

A

B

C

S

Y

Z

SUBJECT INDEX

I

J

K

L

M

I

J

K

L

M

W

X

Y

Z